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PUBLICATIONS FROM
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ARTERIOSCLEROSIS

DISEASES OF THE MEDIA

By OSKAR KLOTZ

PUBLICATIONS FROM THE
UNIVERSITY OF PITTSBURGH MEDICAL SCHOOL

PATHOLOGICAL LABORATORIES

ARTERIOSCLEROSIS

DISEASES OF THE MEDIA
AND THEIR RELATION TO ANEURYSM

BY

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PREFACE.

I make no apology for adding to an already enormous literature on *Arteriosclerosis,* but I ask the readers' indulgence for a possible criticism on the brevity of many discussions. The various processes which concern arteriosclerosis merit chapters for each, but the present undertaking was not intended to assume such pretentious proportions. As it is, the discussion has grown beyond our expectations.

The bringing together of the observations and facts concerning the processes of disease which affect the middle coats of the arteries is to emphasize the importance and frequency of these conditions. For some years attention has repeatedly been directed (Virchow 1856, Thoma 1883, Jores 1903) to the disease of the intima, with but casual reference to the medial scleroses. Heller, Chiari and others have demonstrated the importance of syphilitic mesaortitis, Moenckeberg has pointed out the frequency of medial sclerosis, but much can not be obtained in the literature concerning medial arteriosclerosis as a group disease.

Particularly to the clinician has the subject of arteriosclerosis been a difficult one,—and at the same time the most interesting. The protean manifestations of the disease are such that some type of it is to be observed by every practitioner and specialist. What has been its origin, what are to be the results, are questions which must be answered separately in each case.

It is hoped, that in putting together our own findings with those of others, we have at least to some degree, cleared this difficult subject of some of its underbrush and allowed the more important facts to present themselves.

This work was started in 1905 and was nearing completion when the author, in the disastrous fire at McGill University in 1907, lost the entire materials, manuscript and drawings. To repeat the work, recollect the literature, microscopic sections and drawings was disheartening and, I would almost say, uninteresting. The greater part of the practical work was undertaken while the author was associated with the Pathological Laboratory of the Royal Victoria Hospital at Montreal.

I am very much indebted to my former chief, Professor J. G. Adami, for his criticisms and suggestions on this paper. Although, in respect to the nature and cause of intimal scleroses, our views do not entirely coincide, a lengthy discussion on this topic has been omitted as not bearing directly on my subject. For the fuller treatment of intimal arteriosclerosis, I refer the reader to our respective articles in the *American Journal of Medical Sciences,* 1909, and in the *Journal of Experimental Medicine,* 1910.

O. K.

PITTSBURGH, PA.

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ARTERIOSCLEROSIS. DISEASES OF THE MEDIA.

By OSKAR KLOTZ.

INTRODUCTION.

Our knowledge concerning the etiology of arteriosclerosis has been much enhanced by the experimental work done on this subject, and, with the information thus acquired, our views respecting this disease have changed to a considerable extent. It is now realized that the disease, instead of being generalized and affecting the entire arterial tree, (1) may be localized, affecting the arteries of one particular organ, (2) may involve one particular type of artery only, and (3) may be limited to one or other zone of the arterial coat. Not infrequently at the post-mortem table we are impressed by the extensive sclerosis of the arteries of the brain, and the coincident absence of anything approaching to marked involvement of the rest of the arterial system. Nor is it possible for any one to make more detailed investigations of the arteries of case after case, such as those which have formed the basis of this article, without becoming convinced at an early stage that the extent of the disease manifested in the aorta bears no relationship to that found in the peripheral vessels.

With all the advances that have been made, there still remains not a little uncertainty as to how best to classify, that is, to coördinate and bring into relationship the many conditions affecting the arterial wall, differentiated during the last generation, and included under the general headings of scleroses and atheroma. Regarding the intimal changes, it may be said that the more recent studies of Jores and others have established a satisfactory basis for such classification. The same cannot be said regarding the changes in the media. There is still much confusion, both as to the nature and mode of development of these changes, and as to the relationship between medial and intimal disturbances. It has seemed to me timely to make a careful study of the conditions affecting the media, in the hope that thereby coördinating my own observations with those of previous workers, light may be thrown upon the subject. The present study, therefore, is devoted to a detailed consideration of certain disturbances affecting the media.

At the very onset we encounter the difficulty of nomenclature. What general term is to be employed to embrace the group of morbid states included in this study? Some, like Jores, are inclined to lay down that arteriosclerosis is essentially an intimal disease, and one particular order of intimal affections at that: morbid states of the media cannot, they hold, be included under this term. This I cannot but think is too narrow a view. In employing any medical term, we are bound, when possible, to keep in mind its root meaning, and the significance afforded to it by its author. Now "arteriosclerosis" is literally the state of hardness of the arteries, and Lobstein, who introduced the term, employed it to cover all conditions in which the arteries were noticeably hardened to the touch upon clinical examination. Here, I would repeat what I have noted elsewhere, that the hardening of the radials which affords a common clinical diagnosis of arteriosclerosis is due in general to medial and not intimal change. I have thus no hesitation in including the medial conditions here under review, under the heading of arteriosclerosis.

Marchand's recent interpretation of arteriosclerosis, "that in general we must include those changes in the arteries which lead to a thickening of the wall, and more particularly of the intima, in which not only degenerative changes (fatty with its sequelæ), sclerosis and calcification (including calcification of the media) arise, but also inflammatory and productive processes," is very complete. From this definition there remains no doubt that all types of changes in any of the three coats of an artery, which have as a consequence a thickening or hardening of the wall, are of an arteriosclerotic nature; and let us repeat too, that those changes may be either degenerative or productive in kind. It will be appreciated that, on taking this view, the common type of calcification of the media as it is found in the peripheral vessels is also an arteriosclerosis. Savill also employs the term arteriosclerosis in the general sense, and classifies the disease into three types, the intimal, medial and adventitial.

Let us freely admit that, employed thus, the term arteriosclerosis becomes generic and not specific, that several types of arteriosclerosis must be recognized, and so as each type is worked out and its characters definitely known, either a qualifying adjective must be employed to indicate that type, or a special name be given it. Already there is a definite movement in this direction. Thus through the work of Heller, Doehle and Chiari, the existence of a distinct and typical specific inflammatory affection of the media has become recognized, syphilitic mesarteritis (mesaortitis productiva syphilitica), while in order to abolish the confusion in the employment of terms between intimal sclerosis and its later stage of atheroma, Marchand has launched the term atherosclerosis or atherosis, and this has been hailed with avidity by several leading workers in Germany. For myself, I welcome either of these latter words as affording a useful designation for the common type of intimal arteriosclerosis, and helping to differentiate this form from medial arteriosclerosis in which characteristically there is not encountered atheroma proper. In dealing thus with the different types of medial arteriosclerosis, I shall not follow the time-honored custom of leading up to my subject by means of an historical introduction. To do this, to recount conscientiously the successive observations that have been made upon the part played by the media in the development of arteriosclerosis, in an era when this was regarded as a single disease, and to appraise those observations at their right value would introduce prematurely, material which must of necessity be repeated later in the orderly study of the different types of medial arteriosclerosis.

It would be better to refer to these early observations in a systematic description of those types of disease. Here, at most, it is fitting that four names be recalled: that of Johnson, who first recognized the existence of hypertrophy of the media, and more particularly of the muscular constituents of the small arteries; of Thoma, who laid stress upon degeneration and weakening of the media of the aorta and larger arteries, as favoring subsequent intimal sclerosis; of Francis Welch, who first described clearly the syphilitic inflammatory type of medial disease; and of Moenckeberg, who made the first serious study of medial degeneration as a separate entity.

A much more satisfactory introduction to our subject will be from the standpoint of arterial structure. It is becoming increasingly recognized that the different parts of the arterial system differ widely in their histological constitution, in that the structure of any given artery is intimately associated with its function—structure and function in fact being largely interdependent. From this, it follows, (1) that the same noxa acting upon arteries of different types will have different effects and (2) that anything of the nature of an adequate knowledge of disease of the arteries—in this case of medial disease—must be preceded by the knowledge of the normal histology of the different types of the arteries. What otherwise would seem to be wholly dissimilar lesions, may be the expression of the action of a common factor; nay, taking a yet broader outlook, and regarding not one coat of the artery alone, but the whole artery; with these pronounced differences in structure, it may be that of functional structure, exercises a decided influence in the course of the disease and the nature of the lesions there attained.

In making the last suggestion, I am passing beyond the limits here set. It is sufficient to lay down that a knowledge of the structure of the media in various parts of the arterial tree must precede any satisfactory discussion of medial disease.

As has been pointed out recently, the type of arterial change (pathological), as well as its extent, depends upon two factors—(1) the work and function of the tissue supplied, and (2) the histological structure of the vessel: we will be obliged to discuss these details at length. We will also show in how far the vessels in different organs differ in their histological structure. This, I have found, influences the nature of the disease, which may arise in the vessel. We are becoming familiar, and this mainly through the work on experimental animals, with the action of different drugs and poisons on the vascular tissues. That certain poisons and toxins have definitely a selective action for certain tissues is well known, and this point too is being demonstrated in the effect of poisons on the arterial wall.

HISTOLOGY.

Anatomically, the arteries are divided into three types, the large, the medium sized, and the small vessels. Under the large sized vessels are included the aorta and its main branches in the neck and abdomen. The medium sized vessels are the secondary and tertiary branches, arising from the first type, while the small arteries include all the peripheral arteries down to the finest divisions into capillaries. This classification of the arteries is an entirely arbitrary one, without any proper delineations of each particular type, and forms an impossible classification in studying the finer structure of vessels.

On the other hand, the arteries have been classified according to their histological structure, and mainly on the nature of the media. The naked eye appearances of the arteries give no clue to the types belonging to the histological classes. We are bound, therefore, to study the structure of the arteries under the microscope, and to determine the structure of each artery, and to place it in its proper class.

In the main, there are histologically two types of arteries, (1) the elastic type, those in which the elastic tissue is in equal or greater proportion to the muscular tissue in the media, and (2) the muscular type in which the muscle elements are in much greater proportion than the elastic fibres in the media. With these subdivisions, the anatomical classification is of no service. The vessels which are included in the latter classification under the large sized vessels do not necessarily belong to a distinct histological class, and the same is true with the medium and small sized arteries.

On the histological picture of the arteries we, therefore, base the division of our arteries, and, although certain vessels belonging to one or other of these types vary slightly in their characters from the main type, these form only subdivisions under the main headings. I hardly think it is necessary to designate these small differences in vessels of certain organs by separate names, since the characters are isolated to the arteries of the particular organ.

Every artery is possessed of three tunics, the intima, media and adventitia: the intima consists of an endothelial layer, with or without connective or muscular tissue layers between it and the internal elastic lamina. The endothelial layer, which lines the lumen of the artery is composed of large flat cells, arranged in a mosaic or pavement fashion. Under normal conditions this layer is but a single stratum, which under pathological conditions becomes heaped up on itself to form a many-layered tunic. That the cells forming the pearly nodules on the endothelium of the blood vessels are, in part at least, endothelial cells, I am fully convinced, but the discussion of this question in this paper would lead us too far afield.

Beneath the endothelial cells of the intima, there is always, save in the minutest arteries, a thin strand of connective tissue upon which the endothelial cells rest. In the larger vessels the quantity of connective tissue present increases with advancing years until the age of twenty-five or thirty is reached. In the newborn the quantity of connective tissue in the intima of the aorta is hardly perceptible, but, as Thoma and his pupils have demonstrated, there is a constant production of fresh tissue of this nature, with an increase in the thickness of the layer until adolescence. From this time onwards, the physiological quantity of connective tissue in the intima remains fairly constant, and any increase must be looked on as pathological.

Of the muscular elements in the intima little need be said at this juncture, though much importance is attached to them in the pathology of intimal arteriosclerosis. These muscle fibres are found only in the larger vessels and form a layer lying next to the inner side of the elastic lamina. These muscle elements are of the unstriped variety and have a longitudinal direction in the artery. I have never convinced myself of their uniform presence in the vessels of the muscular type. Often this lamella is but two or three cells in width, though at other times this muscular layer, which is called the musculo-elastic layer, is of considerable thickness, occupying as much as one third of the thickened intima. Among the muscle fibres there is a fine network of elastic fibrils which have a relation to the internal elastic lamina. There seems to be little significance to be attached to the fine elastic elements as they normally exist in the musculo-elastic layer, but with advancing age, and in diseased, particularly weakened, states of the artery these fibres become increased in quantity and size, and indicate according to their characters, certain sclerotic changes in the vessel.

Under certain conditions of stress the musculo-elastic layer may become uniformly hypertrophied, without, however, there being any diseased condition in it or in any other parts of the arterial coat.

The internal elastic lamina is present in arteries of all sizes and structures, but differs in its nature in the two types of vessels. The media, which is the mainstay of the arteries, and which is the distinguishing point between the smallest arteries and the capillaries arising therefrom, is also to be found in all arteries. This tunic consists in every case of unstriped muscle tissue along with, in some cases, more or less elastic fibres, and to a slight extent, connective tissue. The media is bounded on its outer side by an external elastic lamina, which also varies in the different types of arteries. The adventitia forming the outermost tunic, is made up of varying amount of connective, elastic and musclar tissue. Each of these elements fluctuates in quantity to a very great extent in the arteries of the different organs.

Arteries of the Elastic Type.—The arteries belonging to this class are the aorta, the first portions of its main branches at the arch, the first part of the common iliacs and the pulmonary. As our interest is mainly centered upon the structure of the media, I shall dispense with the discussion of the minute histology of the intima. Suffice it to say that the intima in the arteries of the elastic tissue type is of far greater importance than in those of the muscular type. And further the structure of the intima in the former is the more complex, and embraces more tissue elements than is found in the latter. The endothelial lining which is common to all vessels occupies the innermost layer and lies upon a slight amount of supporting connective tissue, followed then by a layer of longitudinally placed muscle fibres, as has been described above. These muscles fibres are separated from the media by the internal elastic lamina, which is usually considered a part of the intima.

However, it is not accepted by all that the internal fenestrated membrane belongs to the intima. Donders and Jansen express the opinion that all parts of the vessel wall containing muscle elements belong to media, and v. Ebner points out that there is no sharp division between the intima and media. He is, therefore, inclined to side with the histological subdivisions given by Donders and Jansen.

It is evident that this view is incorrect as has been pointed out by Westphalen and Remak. The coats of the arteries are to be distinguished rather by the direction of the fibres than by the actual elements they contain.

This internal elastic lamina, which bounds the inner side of the media in all arteries, exists in varying quantities, and is often difficult to distinguish from the other elastic lamina present in the media. In vessels of the elastic type, the internal elastic lamina is but the innermost of many lamellæ, which are present in the media. In young individuals this innermost lamella presents no difference from the ordinary elastic rings in the media and lies close underneath the endothelium, with but a few connective tissue cells between it and the endothelial layer of the intima. In adults, however, where the intima has gained in thickness, the internal elastic lamella, too, becomes more prominent and presents a definite boundary zone between it and the media. This increase—it may be the growth of the elastic tissue in general—can be observed with increasing age.

In a child up to three years the internal elastic lamina of the arteries of the elastic type presents a narrow band-like appearance, identical with its neighboring bands in the media. Its characters are the same, and it is of the same size as those in this tunic. At this age it is to be noted that the elastic bands show no branching or splitting of their substance. This branching does, however, occur as age advances. At the age of twenty, the elastic strands have become perceptibly thicker and have sent out a large number of thread-like elastic elements into the neighboring muscle tissue, and this increase in size and number of elastic fibres progresses steadily with age. The process of increase is not confined to the elastic elements of any one part of the vessel, but can be followed in any one of the tunics.

I should like to note here that the splitting of the internal elastic lamina, upon which some (Jores) have laid so much stress, as being the chief characteristic of arteriosclerosis, is not alone confined to this lamella, but similar changes are to be noted in the elastic fibres of the media in arteriosclerotic processes or in old age. To this I shall refer again.

To the outer side of the internal elastic lamina lies the media, a definite structure, well defined on both its inner and outer borders. As the internal elastic lamina bounds the media on its inner side, so the external elastic lamina or Henle's membrane forms its outer boundary. There is this difference, however, that whereas the intimal elastic lamina is normally made up of a single strand, the external lamina may be composed of one or more elastic bands, all of which do not run in the same direction. In the vessels of the elastic tissue variety it is difficult to denote any particular strand of elastic tissue as the external limiting membrane, save that the first elastic layer lying beyond the outermost of the circularly disposed muscular fibres is to be considered the membrane in question, or in other words, the external elastic lamina is the last of the concentric bands of the media. On its outer side, the lamella usually shows a number of offshoots which go to make up the scattered elastic fibres of the adventitia. The external lamina is seldom more prominently defined than any of the other elastic bands of the media; and hence can scarcely be looked on as an individual structure.

The media of these vessels shows the characteristic alternating layers of elastic fibres and muscle bundles. These elastic fibres differ in no way from the internal elastic lamina of these vessels, save that whereas the internal elastic lamina normally sends off few if any ramifications, the elastic elements in the media, although concentrically arranged give off connecting bridges of elastic tissue which weld the tunic into a more compact structure. There are usually from forty to sixty of these elastic rings separated by intervals of 10 to 20 microns.

We have now come to recognize the importance of the elastic elements in the structure of the arteries. In them, we find that the nature and disposition of the elastic fibres varies with the changing function of the vessels. In the main it might be said that where strength and resistance are required in the circulatory system, there is the need of elastic elements. This is not only true in normal vessels but also in pathological states. Thus the large arteries which receive the direct stress of the heart beat are well provided with elastic fibres, while the muscle tissue of less importance for the maintenance of elasticity occupies a less prominent position and is less in quantity.

I would here point out that the conversion of the intermittent blood flow from the heart into a more constant stream, is a work resting to a great extent upon the elastic fibres. In these, nature has provided a tissue which evinces no signs of fatigue, and which is able to take on a considerable reserve work, accommodating itself eventually by a hyperplasia of its own elements. I would point out too that the reverse is the case with the much overworked muscle tissue. The latter is subject to fatigue, like voluntary muscle fibres, and in this stage of fatigue no hyperplasia takes place, but in its place degenerative processes occur, which as I shall refer to later, is of great significance in the medial disease of the arteries of the lower extremities.

The same observations, which were made concerning the developmental change in the internal elastic lamina, are applicable to the elastic rings of the media. In fact, it is to be understood that each one of these rings differs in no essential way from the internal lamina. Thus we are to picture the general structure of the elastic stroma as a system of tubes which fit into each other, and leaving an appreciable space between the contiguous tubes. Another feature common to all these elastic tubes is that they have certain fenestrations which allow communication between the spaces occupied by the muscle elements and, further, allow the passage of the vasa vasorum.

Whereas, the elastic fibres in young individuals up to the age of twelve, are arranged in concentric layers and in life form concentric cylinders about the vessel, with few or no elastic fibrils between the rings, there is with the later development of the vessels the appearance of new fibres which link the elastic rings together and form a network among the muscle bundles. The comparison of an infant's aorta and that of an adult illustrates this variation in the elastic fibres very well. Particularly in old age—even when all evidence of an arteriosclerotic process is wanting—the relative increase in the elastic tissue is evident. Not only do new fibres appear between the concentric rings, but the original elastic strands become thickened and heavier. These changes in old age occur at the expense of the muscle tissue which is relatively decreased and more closely crowded together.

The muscle fibres of the media, which lie between the concentric elastic elements are entirely of the unstriped variety, and these alone endow the artery with active contractile powers. The greater majority of these muscle fibres are circularly disposed, while a few fibres hold an aberrant radial position or stretch lengthwise with the artery. There is but very little connective tissue about the muscle bundles, but there is a fair amount along the course of the vasa vasorum which penetrate the media from the adventitia to its outer third. The individual fibres are spindle shaped, and are about 40 to 60 microns long.

While the elastic fibres are capable of being stretched and then of returning to their former length, they are incapable of contracting beyond this given length. Naturally, therefore, these vessels, of the elastic type, which possess only a partial muscular media, cannot undergo the wide variations in the size of their lumina, being prevented from undue dilatation by the strength of the elastic fibres, and hindered from extensive contraction by the want of sufficient muscular elements and by the impediment offered by the fully contracted elastic bands. This presents the main difference of function between the vessels of the elastic type and those of the muscular type.

Arteries of the Muscular Type.—The arteries of the muscular type include all the medium sized vessels mentioned above and the large group of "peripheral arteries." The main characteristic of these vessels is the large amount of muscle tissue in the media, with but few elastic fibres coursing through this tunic. Although these vessels are more or less deficient in elastic fibres in the muscularis, they have a well marked internal elastic band consisting of a single strand, which after death is so commonly found to lie in smooth folds.

During life this internal lamella is stretched, by the blood pressure, into a smooth band—or strictly, a perfect cylinder, though no doubt between each pulsation it is thrown into wavy folds becoming a corrugated cylinder, by the muscular contraction of the media. That the internal elastic lamina during life lies in a smooth band can be demonstrated by filling a vessel with melted paraffin under a pressure equal to normal blood pressure, and then allowing the paraffin to set while the vessel is hardened. The even contour of the internal elastic band is also noted in cases of calcification of it, when it is found that this lamina lies as a circular lamella, interrupted only at those points where the muscular contraction has ruptured the calcified strands. In diseased conditions of the intima the internal elastic lamina may be reduplicated (Jores, Marchand, Aschoff and others), so that instead of having only a single layer, there are now two or more.

The media in the vessels of the muscular type is composed, in at least nine tenths of its structure, of muscle fibres. These fibres are on a whole of a concentric arrangement, but, nevertheless, have the muscle tissue divided into bundles separated by thin layers of connective tissue. It is in this connective tissue that the fine elastic fibrils appear. The few elastic fibres which are found in the media are irregularly disposed, often forming a fine arborescent network, but never arranged in concentric rings. The muscle bundles, although maintaining a general circular arrangement are frequently obliquely placed, giving greater strength to the wall of the artery.

The muscularis is bounded on its outer border by an external elastic lamina, consisting of one or more well marked strands.

This external elastic lamina is of great importance as it forms the inner border of a highly elastic adventitia. In these vessels the adventitia contains relatively more elastic fibres and muscle elements than in the arteries of the elastic tissue type. It must be noted too that the arteries of the different organs differ in the quantity of elastic tissue they possess in the adventitia. This is well seen in sections of the spleen and of the kidney. In the former the adventitia is particularly rich in elastic tissue, which is true also of the arteries in the uterus while in the kidney less of it is present. The external elastic lamina in these vessels is well defined against the muscular media, almost free from elastic fibres.

Normally while connective tissue elements do not enter into the structure of the media of any arteries to any great extent only such fibres are found which pass between the muscle fibres and muscle bundles to weld a closer union to the component parts. Besides this, there is always a small quantity of connective tissue along the course of the vasa vasorum, which, except under pathological conditions, is of no great consequence.

Similar to the arteries of the elastic type, the larger of these vessels are also provided with vasa vasorum. Smaller arteries, even though provided with the muscular coat, do not possess nutritive vessels, save in the outskirts of the adventitia. In these the thin intima and the more important media derive their nutrition from the lumen of the artery and from the lymph, which is absorbed from the tissues surrounding the vessel. In the larger arteries the absorption of nutritive materials through the intima is inadequate for the demand of the entire vessel. In these the vasa vasorum penetrate from the adventitia into the outer third of the muscularis and by the diffusion of the fluids from these vasa maintain the nourishment of both the outer and middle third of the media. It is only under pathological conditions that these vasa extend their branches beyond the outer third of the media. The inner third of the muscular coat is nourished through the intima from the lumen of the artery. Possibly too this portion of the vessel also obtains some nutrition from the vasa, but I believe that the materials obtained from this source are small.

In evidence that the inner third of the media obtains a nutritive supply through the intima is the fact that when under diseased conditions, the intima is no longer able to carry out its function of absorption and transmission of the fluids from the lumen of the vessel, there occurs in the inner layer of the media, as well as in the deep layer of the intima a degeneration which is usually a fatty one.

It has further been observed that when an embolus or thrombus completely occludes the lumen of a large artery while the vasa vasorum coming in at the adventitia are undisturbed, the portion of the artery containing the obstructing mass shows degenerative changes in the cells of the intima and of the inner portion of the media.

FUNCTIONS OF THE MEDIA.

Dependent upon the structure of the media, the vessels of the muscular type are capable of extensive dilatation, and, on the other hand, of contraction. With a muscle-power which is able to overcome the pressure within the artery these vessels can readily modify the quantity of blood passing through them.

This adaptability is essential to the proper nourishment of the organs and is well illustrated in the vessels of the uterus. During menstruation or pregnancy the uterine vessels dilate to double or three times their normal size, which size is again assumed at the end of the process. This control of the size of the artery (lumen) is alone assumed by the musculature of the media. Naturally these vessels, differing in their essential structure from the arteries of the elastic type, are subject to degenerations and diseases of quite a different sort. The muscular vessels are a more active type of artery, and for their nourishment require a greater number of vasa vasorum. These vasa do not extend farther than through the outer third of the vessel.

Goodall has recently pointed out that after repeated pregnancies the uterine artery is not able to restore its lumen by muscular contraction, and that the diminished calibre is brought about by the development of new tissue within the artery. This new inner tube resembles, in part, the structure of the original artery.

Hence in considering the tissues composing the media of the different types of arteries, we observe that the muscle cells are the most highly specialized cells we have to deal with and they are the cells upon which the functions of the arteries depend. Whereas the elastic fibres form the strength and resisting powers of the larger arteries, the muscle fibres are the active working cells, which control the arterial blood supply. Highly specialized cells are everywhere the cells which become most easily damaged by various injuries and noxae, and so we find here also that the muscle fibres are the most prone to undergo degenerative changes in the media, and it is only in rare instances in which we find the other tissues (particularly the elastic fibres) showing the first degeneration. The unstriped muscle fibres of the media can show all the degenerative changes seen in unstriped muscle cells elsewhere.

Whatever function the various component cells of the media may have, the media as a whole forms the mainstay of the artery. All the variations in pressure brought about by the heart's action act upon and are acted upon by the vessel-walls, that is by the media, and it is only through the resistance of the latter that aneurysms do not occur after great increase in arterial pressure. If, however, the media is deseased and weakened, the vessel wall will not resist normal blood pressure, and will develop in consequence, a localized aneurysm at the site of weakening.

The local weakening in the wall of the media, slight as this might be, was considered by Thoma to be always followed by a little bulging. Relatively this is no doubt true, but one must also bear in mind the earliest changes occurring in the media, and which can be demonstrated in microscopic sections, are not of such severity to cause a giving way or ectasis of an artery. Such slight degenerations may be fully mended without leading to local or diffuse reactions in the other coats.

Broadbent has established the presence of rhythmic contractions in the arteries. These arterial pulsations are independent of the heart beat, and have their origin in the regular contractions of the musculature of the media. Such a system of automatic contractile tubes is of importance in propelling the blood, particularly during diastole of the ventricle.

DISEASES AFFECTING THE MEDIA.

The diseases affecting the media of the arteries can roughly be placed into two groups. The one type, which we will call the productive type is characterized by the production of new tissue cells of whatever character, while the other is essentially a degenerative one, with destruction of tissue as the most marked feature.

It must be explained, however, that in attempting to classify the medial diseases, it is quite impossible to lay down fixed rules which shall govern our grouping. It is so frequently the case that different types of medial disease are present in the same specimen, or again that the presence of one condition, such as a degeneration in some of the elements of the media, has given rise to other changes, it may be fibrous proliferation. It is the unusual to find arterial changes of but one character. Therefore, we must judge the pathological change in a vessel by the predominant features which are present, but not forgetting that the underlying causes may have been of a directly opposite nature.

There is one form of the "productive type" of medial diseases, in which cellular proliferation takes place in the proportional quantities as the tissues exist under normal circumstances, which in other words, is a true hypertrophy or better hyperplasia. On the other hand the newly developed tissue may be made up of one or other of the elements in the media in such a proportion as to overshadow the growth the other cell elements, The tissue, which in the vessels overgrows the other elements, is, as in other organs, connective tissue and represents (*a*) a chronic inflammation, or (*b*) a replacement fibrosis.

It becomes evident that, save for those changes resulting in hypertrophy of the media, the productive type is in truth an inflammatory one—using the term in its broadest sense. The nature of the inflammation and the events leading to it, we must discuss under the various headings, into which this class is divided.

By introducing the process of inflammation amidst the lesions of the media, and assuming a relationship of these with arteriosclerosis, will seem to some a very radical view. However, we must assume sufficiently broad principles to study arteriosclerosis in all the stages of its development, and not alone confine our attention to the end products of the disease. If there is to be any advance in our knowledge of the progressive processes, and if there is any benefit to be obtained from these studies upon arterial diseases there must be a full understanding of the subject from its beginning.

No one will to-day deny that inflammation may assume many characters in different organs, and that the vital reaction to irritants is dependent upon the nature of the irritant and the tissue so affected. That the picture of an inflammatory process of one of the various coats of the arteries differs in some respects from that met with elsewhere, must be recognized, that however the end result of this inflammation is a sclerosis, frequently due to an overgrowth of connective tissue, must also not be forgotten.

It is a question for discussion whether the progressive inflammatory diseases in the arteries should be taught under the heading of arteriosclerosis, or whether only the final product of these diseases, the sclerosis or hardening of the arterial wall should alone receive this designation. This much, however, is certain, that he who wishes to clearly appreciate the meaning and significance of arteriosclerosis, must follow the course of the disease from its earliest beginning.

With this word of explanation, the classification of the medial diseases of the arteries, as given below, will be better understood:

I. Productive including Inflammatory.

1. Hypertrophy of the Media.
2. Acute Mesarteritis.
3. Chronic or Productive Mesarteritis.
    (*a*) Of Bacterial Causation.
        Syphilitic. Chiari's Type B.
        Tuberculous.
        Healed Lesions of Other Infections.
    (*b*) Secondary to Intimal Lesions.
        Chiari's Type A.

II. DEGENERATIVE.

1. Atrophy of the Media.
2. Necrosis of Media.
3. Fatty Degeneration of the Media.
4. Calcareous Degeneration.
    (*a*) Of the Vessels of the Muscular Type.
    (*b*) Of the Vessels of the Elastic Type.
5. Hyaline Degeneration.
6. Amyloid Degeneration.

In the productive or inflammatory type of medial diseases, the process of degeneration, whether present or not, is much less in evidence. One must consider that in all forms of fibroses, there is a process of degeneration in some one of the tissues, of greater or lesser extent, accompanying or preceding it.

Our second group of medial diseases is one in which the degenerative processes come most into prominence. Under various influences one or other of the tissues composing the media is severely injured. At times a single type of tissue is injured consequent to the selective action of the noxious agent. At other times more than one tissue is injured.

Directly dependent upon the amount and severity of the degenerative processes there is usually a certain regeneration of tissue amounting to repair and more commonly connective tissue forms the bulk of the tissues entering into the process of this repair. But on the whole, this regeneration is slower and does not keep pace with the amount of degeneration going on.

It is evident that our classification is an arbitrary one, but one which is very obvious to the histologist. At times one meets with lesions that lie on the boundary line between these two groups, and in which the amount of degeneration and regeneration of tissue is almost equal. These are the rarer findings and do not minimize the value of classifying the medial diseases as we have done above.

The classification as we give it above takes no cognizance of the etiological factors bringing about the disease in question, because it is all but impossible to differentiate the forms of arteriosclerosis by the agent bringing them about. In the first place we must recognize that the various toxic substances do not affect all the arteries in like manner, and that, therefore, a toxic arteriosclerosis may refer to arterial lesions of different histological characters. Our experience in experimental arteriosclerosis has also taught us that the same chemical agent can cause arterial lesions of different kinds, depending upon the amount of the substance used.

PRODUCTIVE CHANGES.

Hypertrophy of the Media.—A true hypertrophy of the arteries without other changes being present is seldom met with, and a uniform hyperplasia of the tissues is equally as infrequent. In 1873 Johnson noted an hypertrophy of the media in the renal arteries in cases of chronic Bright's disease, and this was later confirmed by Ewald, von Leyden and Friedemann. Arteries showing similar changes have been noted by Westphalen in the uterus. Marchand states that such vessels in which the media shows a pure hypertrophy of the musculature without signs of degeneration should not be classified under arteriosclerosis.

Jores noted that the musculo-elastic layer of the intima responded most readily to hypertrophic changes, but in most of these cases the hypertrophy was soon followed by various forms of degeneration. This we have confirmed for both human arteries and those of animals. Savill reports the common occurrence of hypertrophy of the media in persons past middle life.

Sternberg, working in Paltauf's laboratory, observed that in cases of arteritis obliterans, simulating those of Winiwarter and Weiss, a hypertrophy of the media was present.

One finds, however, that other than the isolated observations on the renal, uterine and other vessels, accurate reports are wanting concerning the nature of the hypertrophy in the media. The infrequency of this lesion is due to the fact that the stimuli leading to hypertrophy or hyperplasia of the arterial tissues are seldom so well graded that they do not also cause degenerative changes. If it be given that the nourishment of these tissues is sufficiently preserved, while the stimuli for growth, usually of the nature of increased work, are not too severe, there is obtained uniform overgrowth of all the tissues in the media as may occur in other organs. Such conditions are seen in the uterine vessels of young girls after the beginning of menstruation, and in the same vessels in young adults after first pregnancies. Here all the factors for an overgrowth of the arterial tissues are present, and in consequence a true hypertrophy and hyperplasia of the media is the result. I do not feel convinced that such an hypertrophy ever takes place after the thirty-fifth year.

Concerning hypertrophy of the arteries in general, I am convinced that it is a frequent development, but as it is difficult to gauge a normal standard of thickness for each coat in every vessel, the estimation must remain a relative one, influenced by the personal factor. Nor is it possible to give any opinion as to hypertrophy by counting the number of muscle layers between the two elastic laminæ. With Aschoff we must agree that there is a progressive increase in the size and quality of the arterial coats with advancing years up to the age of thirty-five. This has recently been verified in our laboratory by Foster working under me at the Royal Victoria Hospital. This physiological development involves all the tissues in the coat, although the elastic fibres and the muscle cells form the important elements in the media.

Jores in his studies on arteriosclerosis, in which he placed so much stress upon the development of elastic fibres in the intima, also made some observations on the development of new elastic tissue in the media. He found that where the intima showed such a development of elastic fibres, the media also partook of this change. On the other hand, he did not observe the development of elastic fibres in the media where the intima remained unchanged, nor were these fibres to be observed in instances of progressive mesarteritis.

Meigs is of the opinion that the hypertrophied condition of the media is a diseased and degenerative state. He has noted the increase in the number of muscle cells of the media, but he finds that this is associated with a breaking down of the muscle fibres and other evidences of degeneration.

Arteries with a thickened media are readily subject to processes of disease. Whereas, the process of hypertrophy was stimulated by an increase in function, at a time when the necessary extra nutrition was available, the body sooner or later meets with circumstances in which either the nutrition is not properly maintained or in which the stimuli acting on the media become greater than can be sustained, with a resulting ill-effect on this coat. On the other hand too, if this increased function consist of excessive pressure within the artery hypertrophy continues for some time, until the media, the mainstay of the artery, becomes exhausted and can no longer become hypertrophied nor give rise to new tissue cells. Such exhausted cells allow the vessel to dilate, and themselves undergo destruction. This process of early hypertrophy with a later degeneration can be readily followed in the femoral arteries. In different subjects all stages of hypertrophy, exhaustion, dilatation and degeneration are to be found. The many sacculations found in the vessels of the muscular type, in Moenkeberg's arteriosclerosis, are aneurysmal pouchings which have passed through the above stages.

Concerning the hyperplasia in the renal arterioles there is still much debate. The question arises whether the arterial hypertrophy in chronic Bright's disease, arises before or in consequence of the interstitial fibrosis and hyaline changes in the glomeruli. This question can only be answered by considering the mechanies of the structures under discussion. Moreover under different circumstances other factors have a decided bearing on the subject.

Looking at the glomerulus from a mechanical point of view I should think that it is of enormous importance that so delicate a mechanism should not be subjected to a sudden rise of blood pressure, nor to a continued and excessive pressure. In themselves the glomeruli are unable to exert any controlling influence on the blood pressure. Hence this control must fall on the smaller branches of the renal arteries and their arterioles. The higher the mean arterial pressure, the greater is the need for contraction of these arteries, and the greater is the tendency to muscular hypertrophy to reduce the glomerular blood supply. Whether these arteries contract owing to reflex nervous stimuli or to the direct action of substances of the adrenalin type must at present be left an open question.

In this we, therefore, agree with Johnson that a true medial hypertrophy is found in nephritis. Johnson, however, assumes a kidney lesion antecedent to the arterial changes. His own summary states his position very clearly. "In consequence of the degeneration of the kidney the blood is morbidly changed. It contains urinary excreta and is deficient of some of its own normal constituents. It is, therefore, more or less unsuited to nourish the tissues, more or less noxious to them. The minute arteries throughout the body resist the passage of this abnormal blood. The left ventricle makes therefore an abnormal effort to drive on the blood. The result of this antagonism of forces is that the muscular walls of the arteries and of the left ventricle of the heart become simultaneously and in an equal degree hypertrophied. The persistent over action of the muscular tissues, both cardiac and arterial, is registered after death in a conspicuous and unmistakable hypertrophy."

Gull and Sutton do not agree with Johnson. They believe that the arterial changes in the kidney are conditions common to all arteries of equal size which are or may be independent of renal disease. In other words the lesions in the vessels of the kidney are only a part of a generalized condition.

I do not believe that in all cases the hypertrophy of the media increases the resisting and contractile powers of the vessels. Where the process is a physiological one, as in the uterus, the hypertrophy becomes essential to carry on the increased work to which the vessels are subjected. Pregnancy demands vastly greater blood supply than normally passes to the uterus, and to this increased supply the arteries must accommodate themselves. But once the physiological increase of supply is at an end, the arteries must again accommodate themselves to an inferior work. The vessel walls then contain a larger quantity of tissue, particularly muscular elements in the media, than is required for the normal functions, and these elements which are thrown into disuse are those which become subject to atrophy and degeneration. Hence in these same arteries where we not infrequently note true hypertrophies and hyperplasias we also observe processes of degeneration without any sign of tissue reaction.

Acute Mesarteritis.—Acute mesarteritis is rather an unusual type of arterial disease unless especially looked for with the aid of the microscope. It is but the rare case which is detected by the naked eye, unless the condition has advanced to such a degree as to produce pus foci in the walls of the arteries. On the other hand acute inflammatory conditions are present in the media, in cases of mycotic aneurysms, such as have been described by McCrae. These cases show microscopic evidence of severe disorganization of the entire vessel wall, without the evidence, which one looks for in cases of aneurysm, of chronic changes accompanied by an endarteritis.

Not uncommonly too, the acute progressive stage of mesarteritis is seen to accompany lesions more advanced in repair. Syphilitic aortitis shows very often the progressive inflammation of the media and adventitia about the vasa vasorum, while irregularly scattered through the vessel are plaques of fibrosis denoting a previously acute process. I have only once obtained a specimen of acute syphilitic mesaortitis which did not show any evidence of chronicity (fibrosis). The specimen was obtained from a luetic who died in the late secondaries from an accident. Macroscopically in this case no evidence was present indicating disease of the aorta—and only in section were the lymphocytic collections about the vasa, and the new formation of capillaries in the outer part of the media, indicated. It is to be considered that in every case of syphilitic arteritis there is an acute or subacute stage in which the media forms one of the principal foci. I have twice been successful in demonstrating the *Spirochæta pallida* in these specimens and others have also reported this finding.

Not infrequently a slight and transient acute mesarteritis is present in typhoid (Landouzy and Siredey) and streptococcus septicæmias. The conditions in the media in these diseases is quite independent of any changes which may be present in the intima. Accompanying a streptococcus septicæmia an inflammatory condition of greater or lesser degree is formed in association with the small nutrient vessels of the adventitia and the media, while quite apart from these changes and isolated in areas of the intima away from the infiltrated tissue of the media, are commonly seen superficial fatty streaks. These superficial fatty degenerations of the intima are found in the aorta between the pairs of mouths of the intercostal branches. The significance of these fatty streaks is still under debate although Aschoff favors the view that these are the early stages of arteriosclerosis. This much, however, we can say, that the intimal fatty streaks are not dependent on the inflammatory lesions about the vasa of the media.

Thorel has found that in acute infectious diseases the larger arteries show a small-celled infiltration of the adventitia. Of these diseases typhoid, scarlet fever and diphtheria are most frequently associated with this form of arteritis.

It has been a fairly common observation among clinicians to find thromboses, particularly in the arteries of the lower extremities in cases of typhoid fever. These lesions have been particularly commented upon by the French observers. More recently, however, Thayer has made a thorough study of thromboses in typhoid fever, and has laid particular stress upon its association with acute mesarteritis. He was able to demonstrate an acute arteritis preceding the thrombosis.

Moreover, this author observed that the "radial arteries in old typhoids were palpable in a proportion nearly three times as great as that found in control observations."

McCrae has recently demonstrated acute lesions in the media due to the streptococcus in the course of a puerperal infection. In his case, however, there was present a progressive syphilitic aortitis, and it was found that in the areas of syphilitic arterial change the secondary streptococcal invasion was the most recent and produced further medial degenerations, thereby hastening the development of aneurysm at these sites.

A mesarteritis is commonly present in vessels passing to or in the neighborhood of infected and purulent foci. Larger arteries lying near a small abscess may have only half of their circumference or less showing acute inflammatory infiltration. The process of inflammation may be localized along the vessels of the media or the condition may be diffuse and without regard to the blood supply of the vessel coats. Such vessels are most commonly seen in the lungs in association with infected tuberculous cavities (Pauli). Of necessity these conditions will also lead to inflammatory processes in the adventitia. The importance of an acute mesarteritis associated with abscess formation is that the vessel wall lying contiguous to the abscess cavity undergoes necrosis, with possible aneurysm formation, and at times there is rupture of the artery. Such a degeneration of the vessel wall may result as a direct advance of the necrotic process into the arterial tissues, or from a septic thrombus of the vasa vasorum.

It may be well to note here, that this process explains the presence of aneurysms in and about tuberculous cavities in the lung.

Less frequently one meets with an acute inflammatory process advancing from the intima into the media. Such cases are associated with the deposition of a septic thrombus on the surface of the intima and are usually located at the site of atheroma or atheromatous ulceration (thromboarteritis). In the aorta, mural thrombi are not so rare; in the peripheral arteries, however, the thrombi more frequently encircle the entire vessel and occlude it. In each of these types the septic agents may advance through the intima into the media and there set up an acute inflammation with a diffuse polynuclear infiltration. It is obvious that the presence of a septic embolus may lead to results in the vessel coats, similar to thrombosis.

Mechanical injury without the presence of sepsis is also an occasional factor. Not a few cases are on record of traumatic injury, by bullets, of one or other of the arterial coats, and in all of these cases presenting a secondary aneurysm from such an injury, the media has been severely damaged.

The histological appearance of these vessels differs but slightly. There are, however, the cases in which the acute inflammatory infiltration of the media is diffuse while in others it is localized to the small nutrient vessels passing from the adventitia into the outer third of the middle coat. Again of the latter group there are those in which the inflammatory infiltration is for the most part made up of lymphocytes, as in syphilis and the chronic granulomata, while others are almost entirely polymorphonuclear leucocytes. Save for the granulomatous lymphocytic infiltrations, the character of the inflammatory process gives us but little information as to the nature of the infecting agent. To this I must add, however, that in acute mesarteritis of the vessels at the base of the brain, and particularly in meningococcus infections the leucocytic infiltration is most intense and diffuse—at times so extensive as to overshadow the tissue of the individual layers of the wall. The picture is a very striking one, showing the invasion of the leucocytes, not by way of the blood stream, but by the lymphatic spaces. The question of meningococcus arteritis is well discussed by Loewenstein.

In the lesions produced by severe typhoid fever, the areas of leucocytic infiltration in the media may show evidence of connective tissue proliferation. In these it is seen that the cells, immediately surrounding the vasa vasorum, become large and oval shaped, and between these, cells of fibroblast types are seen. At times too these areas of proliferation are seen to extend closer to the intima than the normal position of the vasa would take them. The intima commonly shows only a slight proliferation of the endothelial cells, with, however, quite a marked fatty degeneration of the musculo-elastic layer. In the more severe typhoid infections the muscle cells of the media show signs of extensive degeneration with a fine fatty deposit in them. These changes accompanied by a productive process are most often seen in the vessels of the elastic type. In a number of cases the bacteria present in the arterial walls have been demonstrated by appropriate methods (Warthin and McCrea).

In none of the lesions of the acute inflammatory type have I ever noted evidence of new elastic tissue formation.

Experimentally various inflammatory lesions have been produced in the media by infective agents (Klotz and Saltykow), trauma, (Malkoff) and thrombi. In introducing living bacteria into the circulation, these organisms find their way into the vasa vasorum and set up inflammatory conditions about them. The histological picture is identical with that found in human arteries in which infection has gained entrance into the medial tissues. Syphilitic mesarteritis has not been reproduced in animals.

The so-called neurotic angioscleroses (Lewaschew) produced in dogs by injury and division of the sciatic nerve must be regarded as an infective lesion following trophic ulcers of the leg. Lewaschew found inflammatory lesions in the media and adventitia of the smaller arteries, but no changes in the larger vessels. In some of the animals experimented upon gangrene of the leg or extensive ulcers developed, which were no doubt associated with the general cellulitis and arteritis present (Czyhlarz and Helbring).

An acute mesarteritis is a serious lesion in the vessel wall, and particularly that type which is persistent and in which considerable destruction (as in syphilis), accompanies the inflammation. Aneurysms both of rapid or slow development are serious possibilities. The milder grades of mesarteritis usually mend readily, leaving more or less connective tissue at the points of repair.

The final stages of acute mesarteritis will be considered under Chronic Mesarteritis.

Chronic or Productive Mesarteritis.—Most of the cases of chronic productive mesarteritis have had a preceding acute stage, and the majority owe their being to infection. Odd cases, no doubt, are met with in which a true acute stage was lacking, and which from the very first were slowly progressive—of the nature of chronic granulomata or in which a replacement fibrosis followed non-inflammatory degenerations. However, it may be said in general, that those factors which produce an acute mesarteritis, as was noted above, are also able to produce chronic fibrosis of the media.

The chronic inflammatory conditions of the media, and it is true also of the acute inflammations, are more commonly found in the aorta and its large branches than in any other vessels in the body. The reason for this lies in the abundant capillary supply to the outer portion of the media of the aorta and the large arteries, while in the smaller vessels these nutrient vessels are few or entirely wanting. In 1844 Rokitansky stated that the intima of blood vessels could not become inflamed, because of the lack of blood capillaries. To-day we recognize an inflammatory condition of non-vascular tissues, and we may modify Rokitansky's maxim, and say that the frequency of inflammatory states of the arterial coats is directly dependent upon the vascularity of the vessel walls.

All are fully agreed, I believe, that we must distinguish between the primary and secondary mesaortitis (and also mesarteritis), as has been fully set forth by Chiari. We would suggest, however, that whereas Chiari has distinguished between two types of medial disease occurring in the aorta, his Type A and Type B can and should be applied to the productive mesarteritis whenever it is found. The features, which distinguish the primary from the secondary production of the scar tissue in the aorta, are applicable to all the arteries.

The secondary mesarteritis or Chiari's type A is the result of, and follows a diseased condition of the intima, an endarteritis chronica deformans. In this instance the mesarteritis is limited to the area underlying a hyperplastic intimal plaque or an atheromatous softening. In this isolated area of the media the vasa vasorum advance from the outer third of the media towards the intima. Evidently the cutting off of the nourishment from the intima by the endarteritis has been a sufficient stimulus to lead to new capillary formation. These vessels are surrounded by a leucocytic infiltration and later heavy strands of connective tissue occupy their environment. With the advance of the vasa vasorum and the accompanying fibrosis, the tissue elements of the media are pushed aside and distorted. The concentric elastic bands are interrupted in their course and the muscle fibres are replaced by connective tissue. Similar changes are also to be found in the adventitia, where it is well seen how the chronic inflammatory or productive tissue follows the course of the blood vessels.

It is, however, less frequent to find a productive *mesarteritis* following intimal sclerosis, than to observe *degenerative changes* occurring in the media underneath endarteritic plaques or atheromatous ulcerations. However, in the event of an adherent thrombus in an artery becoming organized, the fibrous tissue elements which invade the thrombus from the intima, also extend downwards into the media. Moreover the nutrient supply for the organizing mass is obtained to a great extent from the vasa vasorum of the media. These vessels send capillaries to the organizing clot, and along with them there is a considerable development of fibrous tissue. In the event of a later canalization of the thrombus, the walls of the artery remain permanently sclerosed at this point.

In Chiari's productive mesarteritis, Type B, which term he reserves particularly for syphilitic mesaoritis, the chronic inflammation and connective tissue proliferation in the media are primary to any changes occurring in the intima. The changes which occur in the media and adventitia constitute the important characteristics of the disease, while the intimal thickening is only developed secondarily. Type B is particularly characterized by the infrequency of degenerative changes (calcification) arising in the intima, while however, this thickened layer is furrowed and "knotty," and is localized mainly in the ascending aorta. Microscopically, the important changes are found in the media, where granulation tissue and connective tissue form firm masses about the vasa vasorum such as are not present in endarteritis chronica deformans. The adventitia always shows more or less inflammatory reaction about the vasa, while the intima after a time proliferates, after the nature of a chronic inflammation. It is seldom that, early in the disease, macroscopic degenerative processes appear in the media, or if they do, they are very slight in extent. The lesions appear in their whole nature to be the result of a chronic irritation, which is only sufficiently severe to stimulate growth. That a certain quantity of muscle and elastic tissue is destroyed in the media during the progress of the inflammation is not to be denied, but the loss of this tissue is sufficiently slow to allow the growth of the connective tissue to fill in many of the gaps.

In the more advanced conditions where the inflammatory process has spread, the old sites of invasion give place to "gummy" degeneration in which the muscle and elastic tissue appear to melt away. The involved vessel wall is much distorted, and its place taken by granulation tissue, fibrosis and necrosis.

I shall discuss later the point about which there has been some debate, namely, whether the intimal change here is to be regarded as the outcome of the chronic inflammation or as of the nature of a strain hypertrophy.

We have now, thanks to Francis Welch and Heller, become familiar with the macroscopic picture of syphilitic aortitis, so that it seldom escapes recognition. The localization in the ascending aorta, the lack of certain degenerative changes on the surface, the furrowed, thickened and scarred intima combine to form an unmistakable picture. With the microscopic picture of the intima I do not believe we can be so certain. There are other infectious diseases which lead to a small celled infiltration of the vasa vasorum in the adventitia and media, and which on healing leave bands of scar tissue coursing through the tissues of the vessel wall. However, the characteristics of syphilitic mesarteritis bear the same relationship to those of other infectious mesarteritides as the syphilitic cirrhoses of the liver do to other liver cirrhoses. That is in syphilitic mesarteritis the connective tissue bands are much heavier, and more stellate than are seen in other cases.

The macroscopic appearance of the syphilitic aorta in the advanced stage is well described by Malmsten. "The wall of the aorta is thickened. The inner surface is uneven and has diffuse or closely aggregated, round or irregular, more or less circumscribed convex plaques, which on cutting through are seen to consist of yellowish white firm masses, presenting here and there stellate scar-like contractions. This puckering leads to the irregular groovings and warty character of the surface. Besides this sclerogummy process, the aorta shows changes simulating advanced and degenerated syphilitic lesions elsewhere. As regards the localization, the aorta may be attached throughout its entire length or more frequently in the ascending arch alone, or again various areas in the vessel may be attacked leaving clear parts between the lesions. Large calcareous masses or plaques are entirely wanting."

In short, in this stage of syphilitic aortitis all three coats of the artery are affected, the intimal lesions having followed the changes in the adventitia and media. Microscopically we find that the thickened artery owes its bulk to the immense increase in the adventitia along with the thickening of the intima. The media suffers an actual loss and narrowing due to destruction of the fibres of its essential tissues, and is frequently reduced to less than one third its original width.

As we have stated above, the early changes in syphilitic arteritis takes place about the vasa vasorum of the adventitia, of the nature of lymphocytic infiltration about the arterioles and capillaries. Tissue destruction is not evident at the beginning. Lymphocytic infiltrations about the vasa vasorum are also seen very early, and with this there appears a new development of capillaries which course the media beyond the limits of the outer third. As these vessels stretch through the medial tissues there is a concurrent loss of muscle and elastic tissue, while young fibrous tissue accompanies the advance of the vasa. The remarkable feature in the process of the lesion is the rapid disappearance of the fixed tissues (muscle and elastic fibres). These tissues appear to melt away in the environment of the syphilitic virus, but the process of tissue-loss is not so rapid as to leave areas of necrosis patent, but new fibrous tissue is found to keep almost equal pace with the tissue destruction. The areas in which the tissue cells are "melting down," are always densely infiltrated with lymphocytes, plasma cells and fibroblasts. A careful examination of active syphilitic lesions in the arterial wall demonstrates that the muscle fibres commonly undergo fatty degeneration before disintegrating, and that similar changes take place in the elastic tissue. Before final dissolution the elastic strands no longer react to elastin stains.

The vasa vasorum of the adventitia and media frequently show changes quite similar to those in the main artery (Molinari). The intimal proliferation in these small vessels becomes so great as to lead to occlusion of the lumen, and Molinari believes that this produces nutritional disturbances sufficient to cause necrosis of the muscular and elastic elements of the media. The development of granulation tissue and miliary nodules about the vasa vasorum is considered by Doehle, Beck and Backhaus to be miliary gummata. It is but seldom that giant cells are encountered in these cellular aggregations.

This microscopic picture of productive mesarteritis differs widely from the ordinary one of arteriosclerosis, while at the same time it is quite distinctive for syphilis as seen in the aorta. Nevertheless, it must be remembered that other agents (infections) than syphilis can bring about similar changes in the arteries. Thus in several instances Chiari and also Beck encountered lesions of a like nature in individuals in whom both the history and the anatomical findings elsewhere in the body proved negative for syphilis. Chiari states that although a mesaortitis productiva of the Type B may be caused by other agents, syphilis as a factor must not be lost sight of in any case.

Besides producing scar tissue in the media with a secondary proliferation in the intima, syphilis may lead to true gummatous formation in the arteries. Benda and others have observed that the small and medium sized arteries as well as the thoracic aorta are the places most often attacked. The gummata localize in the media or adventitia, where giant cells and lymphocytic infiltrations are found. In the intima the endothelial and subendothelial tissues proliferate, leading to endarteritis, deformans or obliterans. This tertiary lesion of syphilis in the aorta has also received attention from Doehle and Malmsten, the latter of whom referred to it as a "sclerogummyaortitis." The gummy type of lesion carries with it the characteristics of granulation tissue in the centre of which the gummy degeneration is found. Hence we have the combined productive and degenerative processes going on side by side.

The more direct proof of the nature of the productive mesarteritis Type B being syphilitic has been brought forward by Schmorl, Benda Wright and me in the demonstration of the *Spirochæta pallida* in the medial lesions of the arteries. The same difficulty is experienced in demonstrating the spirochætes in the syphilitic mesarteritis as is found with the tertiary lesions of the disease. In favorable instances and earlier lesions the spirochætes are present in large numbers about the lymphocytic collections of the vasa. When older and more advanced changes are present the organisms are found only rarely in the peripheral zone.

It is unquestionable that the organism (*Spirochæta pallida*) and its toxins are directly responsible for the invasive inflammatory tissue of the adventitia and media.

Up to the present, adequate explanations have not been given for the localization of the syphilitic aortic lesions in the ascending limb. The frequency of this site suggests an anatomical reason, possibly depending upon the nature of the blood supply, and the origin of the vasa vasorum of this portion of the aorta.

While so many observations have been made upon the histology of acquired syphilitic aortitis, there had been relatively little work done on changes in the arteries in the congenital form of the disease.

Mracek has noted in congenital syphilis that there are numerous ecchymoses in the adventitia of the larger vessels, while the vasa vasorum exhibit a small-celled infiltration about them. Occasionally too, he noted a slight endarteritis in the carotid, crural and iliac arteries. Buchta has reported a case of congenital syphilis in a young adult of seventeen, in whom the vessels of the arms and legs became cord-like, and greatly impeded the circulation, so that partial gangrene of the foot set in.

Bruhns has recently examined nine cases of congenital syphilis, and has been able to demonstrate lesions in the aorta which are very like the lesions met with in mesaortitis productiva, as described by Chiari in adults. The dilated vasa vasorum in the adventitia showed a constant small-celled infiltration about them, while the condition was also to be traced in the outer zone of the media. The dense inflammatory infiltration of the media leads to a pushing apart of the elastic fibres, so that the structure of the vessel becomes looser in this region. The leucocytic collections in his specimens consisted both of mononuclear and polynuclear cells, while epithelioid cells were also present.

Bruhns concludes that, in congenital syphilis of the aorta, acute inflammatory infiltrations are present in the outer layer of the media and in the adventitia, particularly about the vasa vasorum. He holds that the lesions of congenital syphilis in the aorta are identical with those of the acquired type as described by Chiari.

Wiesner has studied the arterial changes in ten undoubted cases of congenital syphilis in children, and has found constant characteristic lesions in the arteries. According to his findings the aorta with its larger branches, and the pulmonary artery, are the most frequent sites of the pathological conditions. In these vessels he distinguished a boundary zone between the media and adventitia, in which, as is also the case in the arterial lesions of acquired syphilis, the primary alterations in the tissue are to be looked for. He found a constant hyperæmia of the vasa vasorum both in the adventitia and in the boundary zone, while in some cases a thrombosis, and even a hemorrhage, occurred in these regions. The hemorrhages in his cases occurred most frequently in the adventitia. Another constant feature found in the arteries in congenital syphilis is the presence of a round-cell infiltration following the vasa vasorum from the adventitia into the media. In congenital syphilitic children several weeks old, Wiesner found a peri-vascular fibrosis replacing the cellular infiltration, and in some cases an obliteration of the nutrient vessels.

In one instance of a child three months old he noted the occurrence of a connective-tissue production in the media, so that the elastic fibres had almost entirely disappeared in this region. Wiesner considered that this was a later stage of the inflammatory infiltration seen about the vasa of the aorta in new born children.

Recently we have reported a case of congenital syphilitic aortitis in a still-born full-term child. The lesions in this case presented characters similar to those seen in the acquired disease. The ascending aorta and the arch were the site of irregular radiating grooves about which the intima was thickened. Petechial hemorrhages of the media could be seen through the intima.

In the microscopic sections, it was found that the media showed an intense small celled infiltration, localized about the vasa vasorum. This infiltration was also present in the adventitia. Not alone were lymphocytes present about the vasa, but there were polynuclear and epithelioid cells, besides a general diffuse fibrosis, pushing aside the normal tissues of the wall. A necrosis involving the elastic tissue and muscle fibres of the media was present. The intima was much thickened over the altered media.

It was suggested that since the congenital syphilitic lesions of the aorta resembled so closely those of the acquired type in adults, that more than probable, some of the so-called acquired lesions in the arteries which are met with in later life, are of congenital origin.

Recently Scharpff has examined the aortas from a number of syphilitic infants. The specimens which he examined showed no macroscopic lesions, and he was unable to determine any definite mesarteritis in the histological preparations. From his observations Scharpff rather doubts the findings and conclusions of Wiesner.

On the other hand Scharpff's findings only illustrate that in cases of congenital syphilis, aortic lesions are not necessarily present. The same is also true for acquired syphilis.

As has been repeatedly stated above, although syphilis is the more frequent causative factor in the production of a primary chronic mesarteritis, due credit must be given to other infections. I have convinced myself that rheumatism does lead to small areas of medial fibrosis which in many respects simulate the sclerotic patches in the heart described by Aschoff. During the progressive stage of these lesions narrow lines of cellular infiltration are seen along the small capillaries in the adventitia and also in the media. The larger arteries and arterioles of the media do not share this infiltration. Moreover the inflammatory process is limited to a very narrow zone just along the vasa vasorum. Frequently this infiltration is only a few cells deep. As the process of repair advances this area becomes occupied by a zone of fibrosis, which as in rheumatic myocarditis, is very patchy in character. Recently I have been able to reproduce these lesions in rabbits by repeated inoculations at varying intervals of the so-called *Micrococcus rheumaticus*. These experimental lesions I found only in the aorta, and in some instances they were associated with intimal thickenings in the aortic arch.

In typhoid infections although an acute stage, as we have described under acute mesarteritis, is not infrequently found, the process of fibrosis does not so commonly occur. It would seem that although there is an acute reaction about the vasa vasorum in typhoid, the reaction is too slight, and the fixed tissues about the vasa are too little altered to demand the development of new fibrous tissue. It was only rarely that there was any evidence of destruction or of fibrous tissue proliferation about the vasa vasorum.

More rarely do we find a tuberculous infection of the media. Occasional cases of tuberculosis involving the intima have been reported. These latter conditions are most frequently found associated with a previous intimal lesion into which the tubercle bacilli have found their way, setting up a caseating focus (Aschoff). Here and there the aortic wall is involved along with other organs in a miliary tuberculosis which can be recognized by the naked eye, and the infection is found to localize in the intima (Thorel). Blume found such a condition in the pulmonary veins of a child one and three-quarters years old. In all of the reported cases an active or caseating focus has been described which was in close association with or had broken into a blood vessel, leading to a severe tuberculous septicaemia. It is indeed remarkable that in the event of a tuberculous focus existing in the intima of an artery, it is seldom that this focus extends into the media. Indeed it is unusual too that an isolated tuberculous focus develops about the vasa vasorum at a distance from the primary site. Tubercles may and do form commonly in the adventitia of the arteries lying in tuberculous cavities, and in these cases the media shows more or less involvement. Actual tubercles with giant cells and epithelioid cells infiltrate the media; some of these go on to caseation and others to fibrosis, and very often the inflammatory state causes thrombosis of the affected artery.

The multiple miliary nodules which are seen about the minute arteries and veins of the meninges in tuberculous meningitis are not in the walls proper, of these vessels, but have developed in the outermost and loose meshwork of the adventitia.

Some difficulty is experienced in distinguishing tuberculous foci in and about the small arteries. Duerck has recently demonstrated miliary nodules in the vessels of the pia, which macroscopically had the appearance of tuberculosis, and yet no evidence of tuberculosis was present elsewhere in the body, while syphilis was present.

To sum up the important points concerning the productive mesarteritis, we have (1) a type of inflammatory reaction of the media secondary to lesions in the intima, having no definite etiological factor and localized to the tissues lying beneath the diseased intima (Chiari's Type A), and (2) a mesarteritis associated with inflammatory infiltration of the adventitia, primary to intimal proliferation which is most frequently caused by syphilis (Chiari's type B), but which may also be induced by other infections. In both types of productive mesarteritis the newly developed medial tissue, while replacing the tissue proper, seldom shows degenerative changes in progress, either in the area directly affected or in the immediate neighborhood.

Periarteritis Nodosa.—There is a distinct class of nodular inflammatory thickening of the arterial coats which must be considered apart from the usual inflammatory infiltrations of the arteries.

Up to the present there are about thirty cases of periarteritis nodosa recorded. The first description of the macroscopical appearance was given by Rokitansky in 1852, and in 1866 Kussmaul and Maier gave an exact histological description of the disease, and its name. Since these early reports little new has been added to our knowledge of the affection, save to confirm the early observations. The later observers have to a great extent confined their attention to the discussion of the etiology of the inflammatory process, but there is still no uniformity of opinion. Syphilis as a factor is doubtful.

Periarteritis nodosa is a disease of the smaller blood vessels, more commonly found in men than women, and beginning usually at the age of twenty to thirty years. The disease develops as multiple nodules on the small arteries or arterioles, and is most frequently seen on the coronary artery of the heart, or the hepatic, the mesenteric and the renal arteries. Nevertheless, its distribution may be very varied and the vessels in the muscles, lungs or skin are occasionally the sites of predilection. The lesions are to be seen as small nodules appearing on the outside of the arteries, sometimes encircling the artery, at other times projecting outwards as a globular mass the size of a pea. At the bifurcation of a vessel the thickening may be more diffuse, and extend for half an inch or more along the artery. The more distinct enlargements are found on vessels lying in a loose tissue, but nevertheless nodular thickenings are also found on the arteries in the substance of the kidney, spleen, heart and liver.

Remarkable it is that no similar disease has been found in the veins, nor in the aorta or the vessels of the elastic type.

In some instances, and more particularly in the heart, the nodular thickenings of the arteries form a “ rosenkranzartig ” appearances. There appears to be no uniformity in which the disease attacks the arteries. At times the mesenteric system alone is affected, at others the cutaneous or the cardiac vessels. Consequently the symptoms vary widely and the diagnosis is difficult to make during life. With involvement of the gastro-intestinal tract, symptoms of pain and diarrhoea are not unusual features. When the vessels of the heart are affected, and more particularly when the intima of the arteries has taken part in the nodular thickening, symptoms of angina, or of myocardial fibrosis or softening, may arise. Very rarely do the arteries of the meninges become involved in this disease.

Kussmaul found the arteries of the bladder, as well as those of the breast and skin, showing nodular thickenings of their coats. Graf found the same changes in the arteries of the adrenals, while Fletcher described a type of periarteritis nodosa in the vasa vasorum of the aorta.

Considering the wide distribution of the disease throughout the body, it is not a little remarkable that the vessels of the brain are seldom if ever attacked, though Chvostek and Weichselbaum and also Muller have each described cases in which nodules were present on the cerebral arteries. The aorta and pulmonary artery remain fairly immune.

Of the individual lesions in the arteries two types have been described, (1) the solid nodular, and (2) the nodular with aneurysms. These types have received recognition rather from the appearance than from the mode of origin. Both of the types have had the same conditions leading up to their development, but in the case of the multiple aneurysms, the reparative tissue about the nodules has not kept pace with the disturbance in the media and adventitia, with the result that the normal blood pressure could not be sustained. In short, the development of aneurysms is but a stage or a sequel to the disease in general.

There is still some diversity of opinion as to the pathology of the nodules. Kussmaul and Maier, who first described the histology of the lesions, and the majority of the observers (Muller, Veszpremi and Jansco, Freund, Grafared, Longcope) are of the opinion that the lesion is essentially an inflammation, beginning in the adventitia. In the early stages a round-celled infiltration is found along the adventitial vessels, which spreads both into the adjoining tissues and into the media. Lymphocytes are present in great numbers and fibroblasts accompany the tissue infiltration. With the advance into the media the muscle fibres are pushed aside and to a great extent destroyed. The elastic fibres, later, also undergo destruction, and with this weakened arterial wall, aneurysms may be developed. The thickening of the intima which may develop to such an extent as to occlude the artery, is looked upon as a secondary process. The irritation of the noxious agent in the media affords the stimulus for tissue proliferation in the intima.

Later, secondary degenerative changes may occur in this thickened intima.

A few (Fletcher, v. Kahlden and Chvostek and Weichselbaum) held the view that the disease arises in the intima and advances from here into the media and adventitia. The evidence which these authors bring forward in support of this contention is not clear.

Eppinger on the other hand believed that the disease was an unusual condition of congenital weakness of the arterial wall, which in consequence to the rupture of the elastic lamellæ developed multiple aneurysms. The firm nodules, he believed, represented organized thrombi filling the aneurysms and had no direct association with an inflammatory process in the adventitia.

Ferrari, Meyer and Moenckeberg were of the opinion that prior to any inflammation in the adventitia or media, a focal degeneration of the muscle elements of the media was to be seen. Preceding the destructive changes, a peculiar œdematous infiltration between the muscle cells was found, which was later also present in the adventitia. This focal necrosis of the media may later be followed by an inflammatory reaction, or by aneurysmal dilatation which in the advanced condition develops a secondary proliferation of the adventitia.

As a causative factor in periarteritis nodosa, syphilis has been spoken by Kussmaul, Chvostek and Weichselbaum and Graf. But in only a few instances has syphilis been shown to have been present elsewhere in the body. Although it must be recognized, from the description here given, that the lesions are of the same order as those encountered in syphilitic mesarteritis, nevertheless the weight of evidence is against the specific nature of the disorder. Various bacterial organisms have been found in the lesions (Graf and Bombard), but no single infection can be associated with the disease. One must, however, agree with Longecope that in spite of the failure to associate the lesions with a particular kind of organism, there are many features in the disease which suggest an acute infection.

DEGENERATIVE LESIONS.

We now come to the second class of medial diseases, that in which the process of degeneration is much more pronounced than the active repair of the tissues. In some types and instances, repair is entirely wanting, while in others an attempt is made to replace the degenerated areas by fibrous tissue. Hence this type of degenerative lesions does not only include those cases showing pure tissue destruction, but also those in which the primary and extensive tissue destruction has called forth some production of new tissue.

Atrophy.—Similar to atrophic changes in the various tissues of the body, a process of atrophy may occur in the walls of the arteries. This atrophic change is found in the arteries of the various types and affects mainly the media.

Under some conditions atrophy of the arterial coats occurs as a physiological process. In instances where an artery suffers disuse the more specialized tissues in the wall diminish in size and eventually disappear. At birth when the pressure relation of the blood in the pulmonary artery and the aorta are altered, the ductus arteriosus by its muscular walls closes the lumen of the vessel. Thrombi occur only in unusual cases during the closure of the ductus. The intima, however, rapidly closes the potential lumen and obliterates the blood channel by a connective tissue proliferation. Gradually then, the muscle elements of the media diminish in size and number, until they have entirely disappeared and their place is taken by fibrous tissue.

A similar atrophy may be observed in the walls of a thrombosed artery, although the loss of the tissue is more gradual. In each of these instances the factor of disuse is coupled with an alteration of nutrition which plays an important part in the process. Particularly in an adult vessel the sudden shutting off of nutrition, by thrombosis, from the lumen acts deleteriously upon the tissues of the inner zone of the artery opposite the thrombus.

In old age, it is most common to find atrophic conditions associated directly with the altered nutrition of senility. At the same time in which an atrophy or decrease in amount is taking place of one tissue, there is commonly an increase in the tissues of a lower order. This atrophy of certain tissues is an indication of the wear and tear which is taking place from the constant activity of the part. Consequent to the loss of the tissue cells of a higher order, there is a relative—or at times an actual sclerosis. In the arteries, Aschoff speaks of this as an "Abnutzungssclerose"—wear and tear sclerosis. This we believe is a very happy expression for the condition.

Marchand has laid stress upon the close association of nutritional changes with the process of arteriosclerosis. While this explanation is very apt for the scleroses of old age, we feel that there must be some further underlying cause in the numerous arterial scleroses occurring in early adult life. However, this is aside from our main point.

In actual atrophies of old age similar changes occur in the muscle fibres, as are seen in the involuntary muscle cells elsewhere. The individual fibres become smaller and narrower, the nucleus appears granular and has a rough outline. About the nucleus, and particularly at the poles, there is a fine deposit of granular fat or lipoid bodies which form a wedge-shaped cluster. These granules stain readily with Sudan III, but with Nile blue sulphate are colored blue, indicating according to Lorrain Smith the presence of free (or possibly loosely combined) fatty acids.

By the actual measurement of a large series of specimens, Kani has recently shown that the aorta continues to increase in thickness up to the age of fifty. This he considered a physiological process. From this time on however, the vessels were again diminished in thickness.

These results are in agreement with our own observations in which we found that the atrophic change to be seen under the microscope began at about the fiftieth year. These observations are more fully discussed in our section upon Senile Arteriosclerosis.

With this process of atrophy and degeneration of the muscle fibres, the blood pressure within the artery crowds the elastic lamellæ closer together, and leads to a slight—and in actual measurement, imperceptible dilatation of the artery. Practically, every artery of the elastic type shows after the age of fifty a crowding together of the concentric elastic layers. At the same time, while there is a relative increase in the elastic tissue of the media, there is also an actual increase of elastic fibres, due in part to a splitting and feathering of the elastic strands, and also due to the production of new fibres and fibrils in the place of the muscle tissue lost.

Following the slow process of muscular degeneration the sites of the lipiod bodies become occupied by a calcareous deposit, and similar wedge-shaped aggregations of calcareous salts are to be found between the elastic fibres. When such a deposit is present, the muscle fibres have been destroyed. This necrobiotic process we shall discuss again.

Simple diffuse atrophy of the media of the arteries of the muscular type is not so commonly recognized. The process is, nevertheless, just as common as in the vessels of the elastic type, but as the process is decidedly progressive, severe degenerative changes are soon under way. In the iliac, femoral and radial arteries, besides the larger abdominal arteries, there are not infrequently atrophic changes present in the muscular coat. The muscle cells become smaller, the nuclei granular, and the longitudinal striæ appear more prominently. The vessel wall becomes actually thinner, and as the process of atrophy progresses unequally along the vessel, there are small pouchings produced in the wall. As, however, the muscular coat of these vessels is not possessed of concentric elastic bands, there is no reparative tissue to substitute for the degenerated muscle elements, and hence when once started the simple atrophy passes into different stages of severe degeneration. Occasionally there is an attempt at the development of new elastic fibrils, but never are these produced in sufficient quantity to protect the artery from the later stages of degeneration.

Sohma recognized in the arteries of the ovary, an atrophy of the muscle cells in the media, occurring in the vessels passing to the matured Graffian follicles. He believed that this process resulted from disuse, following the extrusion of the ovum of that particular follicle when the requirements of the follicle were diminished. Similar processes have also been observed in the arteries of the uterus following menstruation (Pankow).

It was long ago pointed out by Virchow and subsequently verified by others, that chronic wasting disease, and also chlorosis was associated with a true atrophy of the vessel walls. Not alone is the arterial wall thinned, but in these cases, he says, the lumen of the vessel is itself narrowed. Apparently the blood is diminished in quantity and is lowered in its efficiency of maintaining proper nutrition. Simple atrophy also occurs in the arterial stumps of amputated limbs.

Localized areas of medial atrophy are quite commonly met with both in the vessels of the elastic type and those of the muscular type. Thoma, in pointing out that a weakening of the media precedes the development of an intimal arteriosclerosis, admits that at times the order is reversed. In my own opinion, the latter process, *i. e.,* the primary development of an intimal sclerosis with plaque-like thickening followed by a pressure atrophy of the media, is far more common than the former. We have every evidence in support of this statement. On the one hand, there is in the early stages of endarteritis nodosa (leaving aside the syphilitic) no macroscopical or histological evidence of weakening or disease in the media, and it is only with the progressive thickening and degenerative changes in the intima that the media gives any evidence of change. In some instances this medial change is not truly degenerative—of the nature of fatty, hyaline or calcareous invasion—but the effect of focal nodular pressure is shown in a narrowing of the media at one point. The muscle fibres become crowded together, and in themselves are narrowed; the elastic fibres too are more compactly arranged. In short the normal tissues of the media must accommodate themselves to a nodular overgrowth in the intima, which develops not alone inwards into the lumen of the vessel, but also outwards into the substance of the media. In these circumstances the medial fibres which are stretched over the intimal nodule, no longed possess the same freedom of action of expansion and contraction. It is on account of this inability of free movement that when further degenerative changes occur in the affected media, and more particularly when the process of calcification results, that the tissue elements become fixed in the extended position.

It is quite obvious that the function of atrophied arteries is much diminished particularly as the most active tissue in the media, the muscle, is the first to undergo atrophy. There is a decided decrease in the elasticity of these vessels, consequent to which there are the nutritional sequelæ in other tissues and organs of the body.

Necrosis.—Necrosis of the arterial wall is an unusual feature save when associated with acute infections. These acute infective necroses are commonly associated with an intense cellular infiltration and even pus formation, so that small abscesses are formed in the arterial wall. Such conditions are more properly discussed under Acute Mesarteritis. The infection in these cases reaches the arterial coat by the vasa vasorum about which processes of varying severity develop depending upon the nature of the infecting agent.

Necroses not associated with infection may occur in the artery through the occlusion of some of the nutrient vessels. Nevertheless, it is surprising that when an artery is dissected from its surrounding tissues, necrosis does not take place in the arterial wall proper.

From what we have been able to observe, it appears that the disturbance of the nutrient vessels, as they lie in the adventitia, does not severely effect the health of the artery. On the other hand, there appears to be a system of vasa vasorum which do not come from the adventitial vessels but arise from the smaller arterioles as they take their origin from the main artery and pass through the media. In two instances, both being cases of scarlet fever, we have observed the occlusion by thrombus of the vasa in the media with a non-infectious destruction of the middle coat of the aorta.

Fischer applied the term "arterionecrosis" to the degenerative lesion occurring in experimental adrenaln arteriosclerosis. He believed that the tissue destruction of the media was a process of rapid necrosis in which a final stage of calcification occurred. Shortly following his publication, we were able to demonstrate in his own specimens a process of fatty degeneration which precedes the final stage of calcification.

It is a point of very fine differentiation to distinguish between the rapid process of fatty degeneration with calcification and true necrosis, *i. e.,* between necrobiosis and necrosis. Curious it is, that these experimental lesions in the rabbit are so prone to become calcificied. It is probable that the relatively high calcium content of this animal's blood has something to do with the rapidity in which the arterial changes occur. However, as definite and successive stages can be demonstrated in the process of destruction of the arterial cells in these animals we distinguish this type of disease from true necrosis.

Fatty Degeneration.—In the vessels both of the muscular type and the elastic type, one of the milder forms of degeneration is the granular fatty degeneration of the muscular fibres. In this there is found a deposition of fine granular fat droplets arranged in wedge-shaped masses about the nucleus. The nucleus itself does not show any change in its structure, nor does the muscle fibre appear altered in its size or shape. The fine fat granules are the only evidence which we can find of medial disease. These early degenerations do not impair to any extent the usefulness of the artery, and when the causative agent is removed and proper nutrition again supplied to the media, it wholly recovers itself and the fat disappears from the cell. The connective tissue cells are not altered or stimulated to growth nor are any changes to be noted in the elastic fibres.

When, however, the condition becomes more advanced we find that the fatty degeneration is isolated to patches of the vessel, and seldom is the entire circumference involved in the process. These patches are found to lie away from the vasa vasorum. Close examination shows that the muscle fibres are in all stages of fatty degeneration—from the fine sprinkling of fat in the protoplasm to the coarst fat droplets occupying almost the entire cell body—and the nucleus is found much fragmented. Later the complete disintegration of the muscle cells is also observed in which case the fat droplets lie free and between the neighboring muscle strands. When a number of muscle fibres have become disintegrated and have liberated their fat in this manner, we have a condition in the media resembling atheroma. Such localized areas of fatty degeneration may have an excessive amount of connective tissue developed about them.

When this process is present in the arteries of the elastic type, the elastic strands become pressed together from the force of the normal blood pressure within the artery. Necessarily then the artery becomes thinned at this point. If the elastic fibres are also involved in the degenerative process, the possibility of the vessel yielding and forming an aneurysm at this site is very great. The elastic fibres when they have lost their normal elastic power can only yield to and not repel the pressure bearing on them. Thoma believed that at this stage, when the media was thinned and weakened, the intima compensated for the loss of strength and enlarged lumen of the vessel, by the proliferation of its superficial layer.

Such localized and irregular patches of fatty degeneration in the media occur most frequently in the vessels of the extremities, and it is remarkable with what rapidity such lesions develop. Areas of sufficient size to be seen macroscopically are not infrequent in the femoral arteries. Microscopically, these areas present masses of fat granules, interwoven with a few elastic fibres and some partially preserved muscle cells.

Where this process of fatty degeneration is advanced I have found the presence of cholesterin crystals and fatty acids, both free and combined in the media as well as in the intima.

It is indeed common to observe these lesser grades of fatty degeneration in the media of most arteries of the body. However, the small peripheral vessels show the condition less frequently than it is obtained in the aorta and its main branches. Nevertheless, it is unusual to have this process of fatty degeneration advance to actual atheroma, as soon in the intima. In the intima, the degenerative changes take place in its deepest layer, the musculo-elastic lamella, where there are no nourishing capillaries. The areas of degeneration in the intima are almost always accompanied by proliferative changes in the endothelium and subendothelial connective tissue, which still further cut off the nutrient supply from the vessel lumen, with the result that the atheromatous plaque becomes progressively larger. In the media, the fatty changes begin in small foci away from the vasa vasorum, but sufficient nourishment is obtained to maintain the life of the cells so that complete destruction does not occur. This does not hold, however, for the iliac, femoral, radial and other larger peripheral arteries, where complete destruction of the involved cells does take place, and a fatty calcareous plaque similar to intimal lesions is produced in the media.

Occasionally too it is noted, and this particularly in the aorta, that a fatty degeneration of the musculo-elastic layer of the intima will advance into the inner layers of the media. In these cases the fatty change may be quite severe,—particularly when the intimal disease has become an atheromatous ulcer. In these cases it is usually found that some connective strands have developed in the neighborhood of the ulcer, the base of which rests on the media. The muscle cells of the media, near the ulcer show extensive destruction and fatty degeneration, while the elastic fibres present hyaline and fatty degeneration. Apparent ruptured elastic fibres are frequent, but true ruptured fibres do not occur. The apparent ruptures present this appearance on account of the isolated degenerations in the strands which do not permit the normal elastic-fibre staining.

Weiszmann and Neumann, Manchot and others have noted that in areas undergoing fatty degeneration, the elastic fibres are frequently associated in this process, so that in the later stages these fibres undergo a partial dissolution leaving nothing but the fine granular fat particles along their course. Eberhardt regarded these granular degenerations as artifacts but the later studies of Dmitrijeff and Jores have shown definitely the various stages of a fatty degeneration in these fibres.

According to Dmitrijeff, the degenerations in the elastic fibres of the media are the earliest signs of lesions in this coat, and are also to be recognized more particularly in the inner zone, and later also in the middle and outer zone of the vessel wall. He believes that there is a definite change in the chemical composition of these fibres in the process of degeneration.

That the elastic fibres do undergo a fatty change is not to be denied, but there is still a considerable controversy in what manner this fatty metamorphosis is brought about. Jores has found definite fatty degenerated elastic fibres, and I have noted this condition not infrequently in the internal elastic lamina and the elastic lamellæ of the aorta, and in experimental arteriosclerosis of animals the process is common when sought for. When the elastic fibres show fatty degeneration, they lose their affinity for elastin stains, becoming only a pinkish color with Weigert's stain. With fuchselin the fine fat droplets are seen to crowd the elastic fibres at the degenerated areas. It is generally held that the elastic fibres are non-nucleated structures, without individual powers of reproduction or of carrying on functional metabolism. On this ground, it is claimed by some that since evidence is lacking that proteid bodies can be converted into fat, and all fatty degeneration must be of the nature of lowered cell vitality with accumulation of absorbed fat, it is impossible to recognize a fatty degeneration of the elastic fibres. These authors believe that the fat noted in association with the elastic strands is to be found not in the fibres, but adhering to their external surface. On the other hand, it is shown by others that a fat accumulation may take place in the form of fine granules within the fibres. These authors accept the non-vital nature of the elastic strands, but point out that some substance within the fibres when altered or decomposed has a strong attraction for fatty substances. These degenerated elastic strands are often to be found in the focal patches of fatty change of the muscle cells.

The diffuse uniform fatty degeneration as is so commonly encountered in the aorta is usually associated with conditions of altered nutrition, or with toxæmias. Old age is a common factor in the mild type of the lesion, and the amount of fat present in the tissue of the media increases with advancing years over fifty-five. The lesion is a truly degenerative one, but it rarely leads to serious conditions. Even in such vessels of the aged, which from macroscopic appearance are sound and healthy, and which show no evidence of the common scleroses in the intima, the microscopic examination of the media shows diffuse fatty and calcareous degenerations of the muscle elements. The elastic fibres are rarely involved in this disease, save when other unrelated lesions are also present in the vessel.

In younger individuals toxæmias of various kinds lead to fatty degeneration of the muscle cells from which they may recover themselves. These degenerations differ from the senile type in showing fatty changes without the calcareous depositions, and further in showing a less amount of destruction or loss in the muscle fibres. Whereas in the senile medial arteriosclerosis, the elastic fibres become irregular and show a splitting of the coarser strands along with the development of a meshwork of cross fibres, the toxæmic degenerations show little or no change in the elastic fibres and no crowding of the elastic lamellæ. Severe diphtheria leads to such a fatty degeneration, while more rarely eclampsia, typhoid, scarlet and other fevers have the same effect.

It is also to be noted that long-continued strain upon the arterial wall, such as is brought about by a continued or intermittent high blood pressure has a deteriorating effect upon the muscle fibres of the media which although not to be distinguished in its early stages macroscopically, is nevertheless readily recognizable under the microscope. The effect of continued strain is, I believe, primarily functional exhaustion of the muscle cells and having this mechanical irritant continued upon the exhausted cells leads to organic alterations within the cells. These degenerations are most easily demonstrated in the fat granules which accumulate in the muscle fibres. Other cellular changes are also present but less easily demonstrated with accuracy.

In the human subject it is with some uncertainty that degenerative lesions in the arteries can be ascribed to strain, overwork, or functional exhaustion. In experimental animals, this can be controlled. In selecting young animals of good stock and in healthy condition, one may exclude to a very low percentage spontaneous arterial disease, or lesions arising from causes other than those directly under the control of the operator. Further when proper controls of sufficient number are examined in conjunction with those experimented upon, the possible error arising from unlooked for causes is reduced to a minimum.

It has been previously shown (Harvey, Klotz) that when the arteries in animals are subjected to increased tension by mechanical means, degenerative changes are brought about in the intima and media. The intimal changes are similar to those described by Jores in " true arterio-sclerosis " in man. A primary hypertrophy of the musculo-elastic layer with a splitting of the internal elastic lamina is produced, which is soon followed by a fatty degeneration of the muscle elements. In all respects this intimal lesion simulates arteriosclerosis as seen in the human aorta. Not only does the intima show diseased changes, but the media is also affected. The muscle fibres are altered and undergo fatty and calcareous degeneration.

It is to be noted that although both intimal and medial disease can be produced in the arteries by purely mechanical means, that these lesions develop quite apart from each other, and seem to bear no direct relation in their process of development. At the sites of the medial degeneration, from the earliest development to such lesions leading to aneurysms, there may be little or no change in the contiguous intimal tissue. On the other hand again, the much thickened and atheromatous intima produced in experimental animals is often found to overlie an unaltered media. Here, however, we must point out that in our animals, these two types of arterial lesions developed in arteries of different kinds. The medial degenerations are prone to occur in the aorta while the intimal atheroma was more pronounced in the branches (carotids) of this vessel. In studying such lesions and offering an explanation for their development we must not lose sight of the normal structure and the function of the artery. In the branches of the aorta a reserve power is developed mainly by hyperplasia of the musculo-elastic layer, and when this hyperplasia has once taken place atheromatous changes soon follow (Jores). On the other hand, our experiments of increasing the pressure in the thoracic aorta, have so overstrained the tissues of the aorta to allow little active repair, in consequence of which progressive degeneration is evident in the functional and active tissue of the media. When the aorta, however, was subjected to less strain an intimal hyperplasia of the musculo-elastic layer with secondary development of atheroma was also evident.

The results of the experiments along this line have been directly contradictory to the views of Thoma on the nature and development of arteriosclerosis.

Whereas it is well established that an intimal proliferation does follow a medial change of the nature of an inflammation, Bouchard claims that in those cases lacking the cellular and inflammatory infiltration of the media, the intimal hyperplasia is of the nature described by Winniwarter in endarteritis obliterans. This latter disease is regarded as a primary affection in the intima, having no association with medial changes.

Dmitrijeff believes that degenerative changes arise in the elastic fibres of the media in the earliest stages of the disease. In the event of an intimal disease being present, these degenerations are first to be found in the innermost layers of the media, but later similar degenerations also occur in the middle and outer zones. The changes in the elastic fibres is mainly one of staining reaction, which Dmitrijeff believes indicates a chemical change in the substance of the fiber.

Such variations in the staining of the elastic fibres often gives the appearance of a rupture of their continuity, as has been contended by Zwingmann, Waegner and others. It is seldom that true rupture of these fibers is to be found, save in association with ruptured aneurysms. Most frequently, as is the case in syphilitic aortitis, the elastic fibres have in focal areas entirely lost their selective staining powers, and appear to come abruptly to an end. Nevertheless these fibres have small unstained strands uniting the apparent broken ends.

Save in the experimental production of severe arterial lesions, in which aneurysms had developed and in ruptured mycotic aneurysms I have never found undoubted ruptured elastic fibres. In human arteriosclerosis, where by the use of Weigert's elastin stain alone, there appeared many apparent ruptured elastic fibres, many of which exhibited the characteristic brush-like end, I have been able to demonstrate the intervening degenerated segment containing either fat or a hyaline substance. The fibrillation of the so-called ruptured elastic fibre is a process more or less common to all degenerating elastic tissue.

With our present knowledge of the nature of elastic fibres it is difficult to say what is the fate of degenerating elastic tissue. Although we are aware of the deposition of fatty granules, of calcareous salts and of a hyaline change in the elastic fibres, we cannot trace the steps in the process of the gradual melting away and disappearance of this tissue.

Calcareous Degeneration.—Closely associated with the deposit of fat in the arterial wall, whether in the intima or in the media, is the calcareous degeneration.

Some years ago we brought forward evidence of the direct chemical relation between the primary fatty degeneration and the deposit of calcium salts in the tissues. Certain features of this contention were opposed, but we believe on insecure grounds. As in all degenerative processes, there are varying stages of the condition until the fully matured chemical reaction has taken place. So, too, in the process of fatty degeneration, and particularly as the meaning of this term is to be observed today, a lowered vitality of the cell with an accumulation of fat products,—there are all stages of fat accumulation, first taking place in a partly damaged cell, and if the process is continuous, increasing until the life of the cell is so damaged that it can no longer attract materials to it. When a cell has reached this low ebb of its life processes, it usually goes on to complete destruction, liberating its stored up contents. It is this liberated fat which is acted upon by the tissue enzymes and gives rise to free fatty acids, which attract calcium salts. It is probable that at no stage in the process of fatty degeneration, and while the fat is still within living cells, do calcium salts enter a reaction with the fatty substances. Hence in such tissues where the fat is still contained within living cells, no excess of calcium is to be found. On the other hand also, as we have previously pointed out, the chemical changes are not complete when the calcium is precipitated by the fatty acids. A succeeding stage is found in which double salts of calcium with fatty acids and carbonates or phosphates are found, and in this condition no difficulty is obtained in demonstrating the presence of calcium, fatty acids and carbonates or phosphates in the same material. If, however, a still later stage is examined, it will be found that the fatty acid portion has been entirely replaced by the phosphatic and carbonic acid radicals, and as Wells has pointed out, the phosphates and carbonates of calcium exist in these masses in about the same proportion as in bone.

Whether the calcareous degeneration occurs in the intima or in the media, it is found that the nature of the process is the same.

However, although the stages of the calcareous degeneration of the arteries are the same for those of the muscular and of the elastic type, the histological picture of the deposition of calcium salts differs somewhat in these.

The clinician constantly meets with arteriosclerosis in the vessels of the extremities and not infrequently is confronted with grave disturbances of nutrition as sequelæ. These vessels of the muscular type become rigid and inelastic and are unable to properly control the blood supply of the part. Thromboses, with resulting gangrene, are the dreaded outcome of these diseased arteries.

Similar lesions to those present in the palpable arteries also develop in the vessels of the internal organs (uterus, spleen, thyroid and mesenteric arteries).

When examined in the early stages of degeneration the musculature of these peripheral arteries shows a fatty change, while the intima may remain quite normal. The muscle fibres are first attacked and later the elastic fibres are also involved, until eventually the process exhibits a fatty degeneration or destruction of all the elements in the area attacked. Seldom do we find the pure fatty degeneration proceed to this stage without the presence of associated calcium salts within it, and at the same time fatty acids, both free and combined, may be demonstrated.

From this stage on, all grades of calcification of the arteries are found. The simpler cases show a granular deposit, the more severe forms show the calcareous salts welded together in solid masses completely encircling the arteries. There is in this process no type of true calcification in living cells. Where calcification exists, there has been a destruction of tissue in whose place have been left the fatty particles of the degenerated cells, so that in some stage of the calcareous degeneration of the arteries, a fatty process can be demonstrated, and that in the progressive process of calcification only small quantities of fatty acids free and combined are to be found. It is not fully understood whether the doubly refractile particles described by Adami and Aschoff, have anything to do with the liberation of free fatty acids which combine with the calcium salts. In these calcified areas the calcium phosphate is much in excess of the carbonate (Wells), which allows the demonstration of these salts by von Kossa's method with silver nitrate. This method is still the best to demonstrate the presence of small quantities of calcium (phosphate) in the arteries. Larger quantities of fatty substance in and about the calcified areas than are exhibited by the direct application of Sudan III, are obtained if the areas are first decalcified. It is found that some of the calcium salts are linked to the fatty substances and thus prevent the fat from staining with Sudan III. This has been best shown in the experimentally calcified arteries of rabbits.

It is not infrequently noted that the vessels of the muscular type may be so completely calcified as to present rigid tubes, which can be grasped at one end and raised without kinking. This process, regardless of the etiological factor, has no connection with the intimal arteriosclerosis in other parts of the body, though nevertheless the two may and do occur in the same subject, and we must agree with Moenckeberg and Marchand that the presence of arteriosclerotic changes in the radial and other peripheral arteries is no proof of arterial disease in the aorta or other internal vessels.

This process of calcification of the peripheral arteries bears no relation to inflammatory conditions in the media, and is always a degenerative process from the beginning. What relationship there may be to alterations in the vasa vasorum remains undecided. It may be that the isolated and patchy way in which the degenerated areas arise, have their origin in endarteritis or thromboses of the vasa vasorum by which means the nutrition of the media is severely interfered with. We do know, however, that the calcareous degeneration of the peripheral arteries is sometimes the result of overwork and high blood pressure within them. This is evident in individuals whose continual occupation requires excessive use of certain limbs. In most individuals the femoral arteries are most frequently affected, while in the upper extremities the right radial shows a greater involvement than the left (in right-handed persons). We have repeatedly demonstrated the extensive sclerotic conditions of the iliac and femoral arteries in individuals (as policemen) who are much on their feet. In females over forty years the uterine arteries commonly show calcification of the media. All these vessels are such as from time to time are taxed by repeated increase of blood pressure, which necessarily must be withstood by the media.

In studying the question of arteriosclerosis (medial) in its relation to occupation, we have been impressed by several points. It has become quite evident that the vessels supplying those regions which are most active are more subject to degenerative diseases than the corresponding vessel of the opposite side. This is likewise true of the vessels of the internal organs, when one of a paired organ (kidney) is functionating more actively than the other. In these cases, we are led to conclude that the process of degeneration follows a condition of overstrain which has been long continued. The condition of overstrain may result from increased blood pressure brought on by circulatory disturbances elsewhere in the body, or the artery itself may be in a condition of " hypertonus " (Russel). In any event, a continuation of either condition leads to a fatigue of the arterial wall with a slow process of degeneration beginning in the vessel. As strain acts mainly upon the media of the artery, it is this coat which suffers when fatigue sets in. These processes of fatigue indicate nutritional and functional alterations in the muscle fibres, which are best demonstrated by the fat droplets aggregated about the nucleus. Still more severe alterations in the muscle fibres lead to the deposition of calcareous salts in the debris of the injured cells.

An analogous type of medial calcification also occurs in the arteries of the elastic tissue type. Here, where the muscular bands of the media are separated by lamellæ of elastic fibres such a firm calcification of the muscle tissue cannot take place. It is almost constantly found, as I have described elsewhere, that in persons over fifty years of age—and frequently in those over forty-five—the media of the aorta shows microscopically calcareous degeneration. In such aortas I have frequently noted the absence of any macroscopic change in the intima or the media, and yet have found that microscopically there was an extensive loss of the muscular elements, their place being taken by a fine, granular deposit of calcium salts. This calcium deposit lies between the elastic lamellæ, and in the sites where the muscle elements have disappeared. In these cases too a fatty degeneration can be demonstrated in the muscle cells which are undergoing necrobiosis. The calcium deposit is readily demonstrated in frozen sections, treated with a five per cent. solution of silver nitrate and counterstained with safranin, or it may also be seen in well-stained hæmatoxylin preparations. The calcareous degeneration of the muscle fibres is limited more or less to a band occupying the middle zone of the media. That portion of the media lying close to the intima, and that layer bordering the adventitia are free from degenerative processes, and in these parts the muscle cells are well preserved. It is also striking that the muscle elements about the vasa vasorum, no matter in which portion of the media they are found, are without degenerative changes. From these evidences and the fact that the degeneration occurs constantly in old age, without regard to any particular etiological factor, I was led to conclude it to be a true senile arteriosclerosis. There is no arterial disease which truly deserves the name of "Abnutzungs Arteriosclerose" (Aschoff) more than this. This senile arteriosclerosis results from gradual loss of nutrition and the long period of work,—the true rust of life. No doubt, in the autumn of life, the cells of the intima and the elements of the vasa vasorum are less active in distributing nourishment to the vessel wall. Not uncommonly the vasa vasorum of these arteries show definite changes and thickening. The lymphatics too in all the coats of the artery become clogged, to the disadvantage of carrying off the effete products. Necessarily then that part of the arterial wall farthest away from the supply of nourishment will suffer the most,—and this is the middle layer of the media.

This calcareous degeneration of the media is distinguished by being uniformly distributed in the middle zone of all parts of the aorta, and in being deposited in fine sand-like granules which are evident only after treatment with silver nitrate, and by the microscope.

True atheroma with its sequel, calcification, is a process beginning and usually confined to the intima. Every now and again, however, we meet with this condition in the aorta, so advanced that the vessel in general appears very shaggy. The intimal surface is rough, and small firm splinters of calcified plaques project into the lumen. The vessel wall is commonly very brittle and its tissues appear dry, so that different layers can be peeled from the surface. If we examine such a specimen, we find that in many places the extensive atheromatous process with calcification lies not only in the intima but also in the upper layers of the media. In such instances, this degenerative process of atheroma has advanced to the middle coat from the intima. It is only in such secondary medial processes that atheroma is found in the middle coat. True atheroma with its calcification seldom if ever arises primarily in the media.

Bone and Cartilage in the Media.—The literature contains a considerable number of reports of the finding of bone in the tissues of the arteries. Very little reliance can be placed on the reports of "ossified arteries" prior to Virchow's discussion in 1862, in which he sets forth the differentiation of "calcification" and "ossification." Many of the older writers used the expression "ossification" very loosely, referring to both the process of bone formation, and of calcium deposit.

At first sight it may seem out of place to discuss the subject of bone and cartilage formation in the arteries, under the "degenerations." At the outset we must admit that here our classification is open to discussion, but after considering the processes involved in these lesions, we felt justified in entering the discussion immediately after the calcareous degenerations rather than with the productive processes.

Rokitansky, Andral and others refer to the occurrence of bone in the aorta as a common finding, but these authors did not make it clear that they were not dealing with calcareous plaques. In 1862, Virchow not only pointed out the difference between ossified and calcified tissue, but he described an actual case of bone formation in the arterial wall. As the instances of true bone were unusual, Virchow's findings were for a time denied (Rindfleisch). Nevertheless heteroplastic bone was demonstrated in various organs in the body and in muscle tissue, and soon after new cases of osseous and osteoid tissue in the arterial walls were described by different authors (Orth, Ziegler, Cohn, Rhoemer and others).

When we review the instances of bone formation in the arteries, we find that the majority have occurred in the media, while the remainder have developed in the intima. In all instances regardless of the site, this new bone develops in the region of previous disease, and usually there is evidence of former calcification. Moreover, when the lesions are observed during their progressive stage, there are evidences of connective tissue and vascular proliferation in or about the calcified area.

Cohn observed that the process of bone formation in arteries developed in two stages, (*a*) a fracture of the calcareous ring in the media with a secondary granulation tissue, and (*b*) the development of osteoid tissue with marrow spaces. The osteoid tissue he believed resulted from a metaplasia of the connective tissue. Bensen describes bone formation in the calcified media of the vessels of the leg in a case of diabetes, and other instances in the same vessels are given by Rhoemer, and by Buerger and Oppenheimer.

Moenckeberg systematically examined a hundred cases of advanced arteriosclerosis and found bone present in ten per cent. of the vessels. Similar observations were made by Howse, O'Brien, Marchand and others.

In a few instances the areas containing the bone deposits were found to be surrounded by cartilage (Rosenstein, Marburg).

As an accidental finding, and in no way suggesting the incidence of the process, I have observed bone formation in the media in two cases, and once in the intima. In the latter instance an old thrombus occluded the vessel, while in the former cases the arteries showed a very marked Moenckeberg arteriosclerosis.

It is extremely interesting that these lesions have been reproduced in animals by a few investigators. Sacerdotti and Frattin were able to demonstrate bone in the renal arteries three months after these vessels had been ligated. Harvey obtained the same results by painting a solution of copper sulphate or silver nitrate on the outside of the aorta of rabbits. Harvey reports that bone with Haversian canals developed in the tunica media in areas which had previously been extensively calcified and that a tissue not unlike cartilage was also formed.

All authors are not agreed upon the mode in which the bony tissue is developed. But the observations are fairly constant indicating that a process of extensive calcification precedes the osseous deposit. Some believe that the mere presence of the calcareous nodule attracts the vascular structures to it (Rhoemer), others consider that fractures in the calcified masses offer the stimuli for the development of a callous-like development, which carries with it blood vessels and connective tissue (Cohn, Paul and Bunting).

Opinion is also divided as to where the bone cells arise which surround the area of initial calcification. Some argue that the bone cells can arise only from cartilaginous or osteogenic tissues, and that those in the arteries must arise from the usual foci of bone cells (Ribbert, Busch and Hansemann). On the other hand the majority of investigators are convinced that bone cells may be derived in a process of metaplasia from connective tissue. In the case of the bone formation in the arteries it is evident that the young granulation tissue which advances to and surrounds the primary calcification plays a very important function in the future development of bone. During the process, the connective tissue cells become closely opposed to the calcareous masses, and transitions can be observed between the adult fibrous tissue cells and the small bone corpuscles. Giant-cells, osteoclasts, osteoblasts and bone cells are all to be observed. At times the new structure contains no lime salts (osteoid), though the cellular arrangement is that of bone.

There seems little doubt that connective tissue may become endowed, if the proper stimuli are present, with the properties of bone cells. From the observations made on bone in arteries, the stimulus lies in the presence of calcareous masses surrounded by granulation tissue. At the points of contact, the connective tissue cells lying against the lime deposit take on the characters of bone corpuscles.

Hyaline and Amyloid Degeneration of the Media.—Two other types of medial degeneration of arteries are very interesting, but, as we have stated above, hardly come under the term arteriosclerosis, unless the word is used in the broadest sense. These are the hyaline and the amyloid degenerations.

Although these two types of degeneration occur under widely different conditions, yet they have some features in common. Both occur in the arteries of the muscular type, and seldom, if ever, develop in the aorta or its main branches. Both occur in the deep portion of the intima, or associated with destruction of the muscle cells of the media.

Little is known as yet concerning the nature and origin of these substances, and still less is known of the manner in which they are deposited. It may be that there is some chemical relationship between the hyaline and amyloid deposits.

Some confusion has developed in the use of the term hyaline, so that we find in histological descriptions of tissues, a considerable variation in the meaning inferred. The word hyaline has come to be used to express any bland or homogeneous appearance, without reference to the nature of the substance under discussion. Though the chemistry of hyaline bodies is not determined, they probably belong to the phosphorus-free glycoproteids, and result from the breaking down of cell protoplasms.

The hyaline deposits found in the media of arteries bear no relation to the homogeneous looking connective tissue so often seen in the pearly plaques of endarteritis deformans.

Hyaline degeneration of the media is most commonly met with in the arteries of the ovaries and uterus, and less frequently in the arteries of the thyroid, spleen and adrenal.

Clark, in 1900, studied the arteries of the ovary, and found that during the development of the corpus luteum, new arteries advanced to this body. These vessels remained active during the progressive changes in the corpus. As soon, however, as the corpus luteum showed degenerative changes, the arteries passing to it showed hyaline changes in their walls. This hyaline change began in the adventitia and advanced into the media. The muscle fibres of the media apparently break down and the detritus of the different cells fuses into one homogeneous mass. Before the mass is properly fused, the degenerated material is quite granular, and contains considerable quantities of fat. Woltke described similar changes in the ovarian arteries, which were not associated with degenerating corpora lutea.

Boeshagen found that the hyaline degenerative process was at times so extensive that the media and adventitia were completely replaced by a hyaline substance, and that the endothelium alone clothed the lumen of the vessel. In some instances he found a newly developed layer of muscle fibres inside of the hyaline substance, so that it appeared to him that a new vessel had formed inside of the old one.

In studying the vessels of the uterus, Szasz-Schwartz observed that the musculature of the arteries was at times replaced by a substance having some of the qualities of elastin. These degenerations are shown to occur most commonly after repeated pregnancies

(Pankow). This author has also shown that proliferative changes similar to those in the ovarian arteries develop a new layer of muscle fibres beneath the endothelial layer, and diminish the size of the lumen.

Similar reports of the hyaline degeneration of the media of the arteries of the ovaries and uterus have been made by Sohma and Goodall respectively. Goodall however believes that the degenerative changes are closely associated with alterations in the internal elastic lamina.

Mention must also be made of the peculiar hyaline deposit which takes place particularly about the vessels in some tumors. In certain peritheliomata there is found a narrow layer of hyaline material immediately outside the endothelial cells of both the capillaries and the smaller arteries. In the latter vessels the hyaline substance may invade and replace the muscular tissue entirely.

Although amyloid degeneration of the arteries bears some relation to the hyaline degenerations, it has some characteristic features which differentiate it. It consists in the deposit of a homogeneous firm substance which, when present in large quantities, can be recognized by the naked eye. When smaller quantities are present, their appearance can be intensified by certain reagents (iodine, or aniline dyes). It is found however, that the amyloid deposits which do not give constant microchemical color reactions, differ in their composition.

Amyloid deposits are more commonly found in association with chronic suppurative conditions or progressive chronic infections. In these instances the amyloid degeneration does not occur about the suppurative process, but in organs and tissues in remote parts of the body. The kidney, spleen and liver are especially prone to be affected, while less commonly is the mucosa of the stomach, intestine, œsophagus, trachea and bladder involved.

In the former instances, the deposit takes place in and about the vascular channels, while in the latter, it bears some relation to the epithelial structures. In the kidney, spleen and liver the early amyloid deposits occur about the walls of the capillaries, immediately outside of the endothelial tube. With more extensive deposits, the amyloid substance is also found in the chinks between the connective tissue cells. The arterioles also become involved, and an amyloid deposit results in the media. Here it is found that the homogeneous substance infiltrates the middle coat and lies between the muscle fibres, but not actually invading the cells. Gradually as the accumulation becomes very extensive, the muscle fibres are compressed and have their nutrition interfered with. A secondary atrophy and degeneration thus takes place in these cells.

When the degenerative process is advanced, the entire media may become replaced by amyloid substance, so that a thick band encircles the vessel. The intima frequently becomes thickened by a connective tissue hyperplasia, and the lumen of the vessel is narrowed.

Little information is at hand concerning the process of amyloid deposit, nor is its chemical nature at all clear.

EXPERIMENTAL MEDIAL DISEASES OF ARTERIES.

Our knowledge concerning the process and progress of medial disease of arteries has been much enhanced by the studies on experimental arteriosclerosis. By this means known agents were administered to different animals over definite periods of time and the effects of these agents on the circulatory system was observed. To prove of value, all such experiments had to be controlled by untreated animals living under the same conditions. In our own experiments, only animals bred from our own stock were used. Moreover, the control animals were "brothers" from the same litter, so that the ages of the animals were equal. As nearly as possible animals of equal weight and rabbits from seven to eight months old were selected. At the conclusion of each experiment, due care must be taken to examine at autopsy for any intercurrent disease.

In our healthy stock of animals, where no aged or previously experimented animals are used, we have not met with spontaneous arterial disease in young rabbits. Like others we have noted the presence of isolated medial plaques in old animals.

We agree with many that great care must be taken in comparing the results of experimental arterial disease, with arteriosclerosis of man. This statement likewise holds for all experimental work on animals, but, nevertheless, when the facts of the experiments are properly arranged, and when the various observations have been duly weighed, we are able to arrive at some conclusion respecting the process or processes at work in the given experiment. If any of the truths obtained in the experiment have a broad significance, it may be that we may then apply them to similar processes in man.

We can by no means agree with the pessimist and the destructive critic that experimental arteriosclerosis and the study of arterial diseases in animals throws no new light upon arterial diseases in the human subject.

By experimental means there have been reproduced types of arterial disease, analogous to almost every type of arteriosclerosis in man. An excellent review of this work is obtained in Saltykow's comprehensive article.

In much the greater number of experiments rabbits have been used. This for two reasons—on account of the ease with which these animals are handled and controlled, and because, for reasons yet unexplained, arterial lesions are very readily produced. Dogs and cats have been tried with only partial success. These animals respond to weaker stimuli by hypertrophy of the tissues of the various coats, but degenerative changes are not so readily produced, save when coupled with a general derangement of metabolic processes, and more particularly kidney lesions.

Experimental Productive Lesions of the Media.—Fischer and v. Schmieden have shown that an hypertrophy of the media develops when the internal pressure of a vessel is increased. It was noted that when the distal end of the severed jugular vein was united to the proximal end of the artery, there developed not a functional hyperplasia of the intima, but an hypertrophy of the media. In the main the muscular fibres of the vein reacted to this extra strain of arterial blood pressure, while only occasional intimal thickenings of an inflammatory nature were observed. This is quite similar to the process which we have described above as occurring in man, save that in the larger arteries the musculo-elastic layer of the intima may also partake in the hypertrophy.

Other productive lesions of the media, of an inflammatory nature, have been produced by different means. Saltykow, by the injection of staphylococci, besides obtaining arteriosclerosis with atheroma in the intima, found various grades of fibrosis in the media. In some instances small collections of leucocytes were observed, in others the tissue changes were more advanced with connective tissue infiltration.

Similar productive lesions result from mechanical injury to the vessel wall, while the direct application of various drugs to the artery has been shown to lead to a localized inflammation which involves the adventitia and media. The simplest mechanical damage is made by crushing the artery with hæmostatic forceps (D'Anna and Malkoff). A true mesarteritis and periarteritis is obtained.

The production of a septic process close to an artery also leads to an inflammatory reaction in the arterial tissues. These conditions of acute periarteritis have been the common result in transplanted vessel segments. Should the vascular tissues be severely involved with greater or less septic destruction of the adventitia and media, a localized aneurysm may follow.

The nature of the reaction in the media following the inoculation of bacteria is dependent upon the nature of the organism, the numbers of the organism and the resistance of the tissues. By these bacterial inoculations we have learned that different bacteria have a varying selective action on the tissue cells. Streptococcus infection affects mainly the intima in proliferation (Sumikawa and Klotz); diphtheria (toxins) act destructively upon the media (Klotz); while staphylococci produce both proliferative and degenerative lesions in the intima and media of the arteries (Sumikawa and Saltykow).

It is unnecessary to describe in detail the histological changes developing in the different lesions, suffice it to say that they bear a close resemblance to the changes found in man.

Chronic productive mesarteritis has also been produced in animals through the agency of tuberculosis and glanders (Duval). With the arterial changes in experimental syphilis we are not familiar.

Experimental Degenerative Medial Disease.—By far the greater number of experiments aiming at the production of arteriosclerosis in animals have led to this result. The earlier experiments on animals were carried on by using mechanical procedures, and as we have observed above, various grades of inflammation were produced in one or more coats. These experiments only indicated that the arterial wall was subject to inflammation and that the inflammatory reaction of the intima differed from that found in the media or adventitia. The so-called nervous scleroses of experimental animals were found to be nothing else than secondary inflammatory reactions.

It was not until Josue, in 1904, observed that the repeated administration of adrenalin over some weeks, produced in rabbits definite arterial lesions of a degenerative character, that the experimental work in arteriosclerosis received a new impetus. Laboratories had been looking for such a substance, and with the suggestion that the active factor in adrenalin was in its blood-pressure raising action, a great many other drugs of similar qualities were tried. Such other drugs produced lesions quite similar to adrenalin (nicotin, digitalin, hydrastin and barium chloride).

By the use of these substances, we have been able to follow the process of degeneration of the media from its earliest stage. In these experiments, rabbits, too, have served the greatest usefulness, and in these animals the aorta has, on account of the frequency of the lesions, been most thoroughly examined. It has been shown that those drugs, exhibiting an increase in the blood pressure, are particularly prone to attack the media, and to produce in it lesions quite comparable with the medial calcification of the peripheral vessels in man. Although the structure of the rabbit's aorta is similar to that of the arteries of the elastic tissue type in man, and thus is different from the muscular vessels of the extremities, nevertheless, the lesions called forth in these two types of artery are comparable. As I have shown above, there is a medial disease of the aorta in man, which although milder in grade, is of the same nature as the process of calcification in the vessels of the extremities. So here also in the rabbit's aorta, the process simulates that in the media of the human aorta, but is much more severe in type. In the rabbit, not alone do the muscle fibres undergo degeneration and destruction but also the elastic fibres which lie between the muscle bands. In the muscle fibres, the fine granular fatty degeneration at length gives way to a coarsely granular one, until the muscle cell dies and leaves the fat droplets in situ. I must emphasize that these free fat granules have come from broken down muscle fibres, and are not developed by a pressing out of the fat from the serous fluids, as Ribbert would have it in the intima. To be emphasized too, is that these patches of fatty degeneration develop away from the vasa, as is also the case with the areas of fatty degeneration of the heart. Following this the involved area becomes calcified, so that not infrequently the entire aortic tube from the arch to the renal presents an egg-shell like structure. Microscopically, it is seen that the process is localized to the media, while in most cases the intima remains intact. The earlier stages of the process show the calcifying areas to be distributed irregularly in the vessel wall, usually in the descending thoracic, and as the disease proceeds, the neighboring plaques fuse to form larger ones. Like both the aortic and the peripheral arterial (medial) disease in man, the experimental lesions occupy the middle zone of the media. The exact action of these drugs on the blood vessels is still a matter in dispute, some maintaining that the increased pressure which is produced in the arteries is the cause, others that the toxic nature of the substances causes a necrosis of the muscle fibres, and still others that contraction or thrombosis of the vasa vasorum leads to a mal-nutrition of the musculature. In my recent experiments I have shown that an increased pressure in the arteries can in itself produce this medial calcification, besides producing in other vessels (carotid), a true intimal arteriosclerosis, with splitting of the elastic fibres and atheroma.

I have found that when a rabbit is suspended by the hind legs for three minutes every day over a period of one hundred and thirty days, that the media of the aorta shows the same egg-shell like calcification as had been produced in other animals by the inoculation of adrenalin. I found that the blood pressure in the carotids and the arch of the aorta is increased, and that the lesions in the aorta were limited to the parts above the renal arteries and more particularly above the diaphragm. The vessels of the lower abdomen and the lower extremities were entirely free from disease. In short, those vessels which had to accommodate themselves to a high and varying blood pressure showed medial calcification.

One of the characteristics of experimental medial calcification is that the vessel wall as a whole is thinned. This is due to an actual thinning taking place in the media, as a result of the muscle cells becoming degenerated and the elastic lamellæ packed closer together.

To obtain a proper conception of the fatty degeneration which bears a relationship to the calcification of experimental medial disease, one must not only stain the frozen sections directly with Sudan III, but some sections should also be decalcified before the stain is applied. Here it will be found that in those areas in which the calcifying process is not complete, there are abundant fats and fatty acids.

From these experimental lesions one readily sees the lack of interdependency between the lesions of the media and those of the intima. It is true enough that under certain conditions the intimal lesions will lead to medial alterations and vice versa, but it cannot be aforesaid that because a certain agent produced a degeneration in the media that a definite other change must occur in the intima.

The work of Josue has marked a new era in the study of arterial diseases. His successful experiments with adrenalin have stimulated much study and have directed our attention along a new path of thought. Since his original work in 1903, many have verified his results, and others have shown that substances having somewhat similar physiological effects as adrenalin will also bring about medial lesions.

One cannot be but struck by the fact that these substances (adrenalin, nicotin, hydrastin, barium chloride, digitalin), although differing widely in their chemical composition, have a common action, the temporary raising of blood pressure. From a pathological standpoint, they also have a common result, the degeneration of the medial tissues of the arteries, particularly the aorta. It has been a common comment that the arterial lesions produced by these various high blood-pressure drugs are similar.

In the interesting work of transplanting segments of vessels between the cut ends of an artery some important observations have been made. Guthrie has found that when homoplastic vessel segments are rapidly transferred from the donee to the host, very little change may occur in the successful graft. The major part of the tissues of the graft persists and continues to live in the new host. Guthrie finds, however, that transplanted segments which have been in formalin, may functionate as blood channels, but only as passive agents. These formalined specimens act as a temporary framework upon which is built a fibrous tissue coat, while the lumen may be clothed by a new endothelial lining. He has obtained similar results with heteroplastic transplantations of arterial segments. In these instances the muscle fibres of the media are observed to disappear first, while the elastic fibres and connective tissue may remain. None of the changes which have been observed to develop in the transplanted segments show any similarity to an arteriosclerotic process.

Carrel claims to have preserved arterial segments in a condition of latent-life over periods of many days. Such segments preserved in the cold can, he says, again be restored to active life by transplantation into an active circulation. When, however, the arterial segments have in any way been damaged the muscle cells are among the first to show degenerative changes.

ETIOLOGICAL FACTORS CONCERNED IN MEDIAL DISEASE OF ARTERIES.

As may be gathered from what has previously been said, there are a variety of factors which play a part in the production of the medial arteriosclerosis. It had been the hope of many investigators that modern pathological technique and minute studies of arterial disease would find a way of distinguishing the lesions produced by a certain agent from all others. We are familiar to-day that such has not been possible, but on the contrary do we find that many and widely diverse factors produce similar arterial disease. Moreover, it is found that a given agent under different conditions or in different amounts, may produce many types of lesions in the arteries. So we come to recognize that it is quite impossible to indicate from the type of lesion present, the agent which had brought about the result. To this general statement we must admit of at least one exception. Syphilis of the aorta can usually be recognized by the naked eye, and the diagnosis can be further substantiated by the histological findings. Occasionally too, in tuberculosis, tubercles are recognized in the walls of the arterioles, particularly of the brain.

Hence, much as we should like to speak of an alcoholic arteriosclerosis, a typhoid arteriosclerosis, a lead arteriosclerosis, as we do of a syphilitic arteriosclerosis, it is impossible to do so. Nevertheless, we are familiar with a variety of agents which act in a deleterious manner upon the middle coat of the walls of the arteries which may be classified into four groups, (1) infections, (2) poisons and toxins, (3) work, and (4) old age. Besides attributing medial diseases to one or other of these definite agents, there are a certain few pathological conditions, which are not primary in the media but which advance from the intima or adventitia into the media. It is quite obvious that disease processes lying deep in the intima, may overstep the imperfect boundaries between the contiguous layers and advance into media. Particularly is this true of infective conditions and fatty degenerations of intima. These latter conditions probably result from a blockage of the lymph channels passing from the intima into the upper layer of the media, and by cutting off the nutrition from the vessel lumen, bring on slow degenerative changes in the muscle cells of the media.

1. *Infection.*—The infections are probably the most important agents which bring about productive lesions in the media. Both with them as with all other influences, the important point rests in the amount and strength of the dose present. When at times, the infective process is so severe that the tissue elements are unable to react, the lesion has the characters of a purely degenerative one, even necrosis. This is, however, quite infrequent, and is met with only in extensive pyæmic conditions. These suppurative foci in the arteries must be occasionally distinguished from the degenerative lesions produced by the toxins of the bacteria. Whereas, the pyogenic bacteria stimulate inflammatory processes of different grades, the bacterial toxins usually act on the tissues in a destructive manner without stimulating an inflammatory reaction. The toxins of the bacterial organisms act directly upon the tissues of the media, bringing about fatty changes and eventually destruction to the cells. It has been found experimentally that the introduction or the inoculation of the living organisms into the body will at times bring about similar degenerative lesions in the media.

With typhoid fever, the results are somewhat different. Here we cannot definitely dissociate the effect of the toxin, and the result of the bacterial invasion itself. In the human subject, the commonest lesions resulting from typhoid fever are noted in the intima of the aorta, where small fatty streaks develop in the deep layers. These fatty areas probably result from the degeneration of the longitudinal muscle fibres, while at other times a more superficial fatty deposit is found in the subendothelial connective tissue. Over some of these areas there not infrequently develops a slight endothelial thickening. These superficial degenerative processes in the intima are, I believe, the effect of the free poison or endotoxin circulating in the blood. On the other hand the septicæmic typhoid infection is also frequently noted by the presence of inflammatory infiltrations along the vasa vasorum of the adventitia and media. These cellular infiltrations I have not obtained in animals when dead cultures were inoculated and I believe we are right in concluding that the medial inflammatory infiltrations are the result of the invasion of living bacteria. In other words, when the infective agent itself circulates in the blood and this is true of typhoid, para-typhoid, *B. coli, Streptococcus* and *Staphylococcus* infections, and the microorganisms become localized at various points in the body, the tissues of the part react to the bacterial irritation by inflammation. Microscopically these reactions are evident in the accumulation of leucocytes or if the process is healing or healed, the presence of excess fibrous tissue is observed. In the arteries, these accumulations of inflammatory exudates are found about the vasa vasorum of the larger vessels and are met with in the infections above mentioned. The result of these infections of the vascular tissues is the development of sporadic medial disease of the productive type.

There are some instances, however, in which localized infection leads to abscess formation in the media. The fixed tissues of the part undergo necrosis and leave a much weakened vessel wall. Extensive tissue destruction may lead to aneurysm or even rupture of the infected arteries, or in other instances when healing has taken place, the lesion is replaced by considerable scar tissue producing a hardening and sclerosed area at this point.

Occasionally the infective agent reaches the vessel wall, not by a septicæmic process, but by direct continuity through the lymphatics from a nearby septic focus. This type is most often met with in the vessels lying in or about infected cavities (tuberculosis) in the lungs. The process is of importance, as it is one of the frequent causes of rupture of these arteries with fatal hæmorrhage. Those vessels which do not rupture develop small aneurysms in their walls at the sites of the diseased media. Tuberculous mesarteritis may be either of a septicæmic origin or by the direct invasion from a neighbouring focus.

Of the infections which lead to dangerous medial disease, syphilis stands in the front rank. The frequency of syphilitic mesarteritis varies in different countries and in different cities. Heller and his pupils reported its frequent occurrence in Kiel; Baerthleni believed that much the larger proportion of cases of arteriosclerosis up to middle life was due to syphilis (Munich); Edgress found that syphilitic arterial lesions were commonest before the age of forty-six; while from Great Britain we have not infrequent reports of the occurrence of syphilitic mesarteritis among the soldiers. In my own experience syphilitic mesarteritis has been among the less frequent forms, while typhoid and the infectious diseases of childhood were the more common causative agents of arterial lesions in early life. Typhoid is probably the commonest infectious disease of the young adult in the cities of northeastern America and almost invariably the arteries of the fatal cases show the early fatty and degenerative changes of the intima along with lesions in the media of the acute or productive type.

It has been pointed out by several authors that infectious diseases of childhood lead to arterial diseases which may play an important role in the development of true arteriosclerosis of later life. Simnitsky working in Chiari's laboratory found sclerotic processes of various kinds in children who had died of scarlatina. He found that in 48.7 per cent. of the cases of fatal scarlet fever, between the ages of two and twenty-five, showed degenerative changes both in the intima and media but he could find no relation between the intimal lesions and any condition in the media or vasa vasorum.

Weisel confirmed the finding of Landouzy and Siredey, who reported that arteriosclerotic processes were prone to follow infectious diseases. Weisel pointed out that in the diseases diphtheria, scarlet fever, measles, pneumonia, influenza and typhoid, although no naked eye changes may be observed in the vessels microscopic alterations and degenerations are commonly present. Exactly what relations these acute processes of the infectious fevers have to the later and more chronic development of arteriosclerosis, these authors do not suggest.

2. *Poisons.*—We know much less about the effect of poison upon the human vascular system than of infection. Though text-books persist in blaming lead, alcohol and nicotin for certain changes in the arteries, yet definite evidence is not forthcoming to establish this. Particularly have the observations of the effect of lead and alcohol been almost entirely negative in establishing any relation between these substances and arteriosclerosis. It is further to be pointed out that although the general statement that lead and alcohol pro-

duce arteriosclerosis is common, there has never been a definite arteriosclerotic lesion described which was caused by either of these drugs. Experiments have been undertaken on animals with both lead and alcohol and no arterial lesions were achieved (Jores). This appears to me to be strong evidence that at the present time we must be very guarded in crediting either of these substances with this severe charge. In the case of nicotin the charge is somewhat different for although in man we have not been able to establish a definite lesion as the result of tobacco, we have, however, in animals, been able to produce arterial degenerations with both nicotin and tobacco smoke. These lesions have been medial degenerations, of the same type as those produced by adrenalin (Adler and Hensel).

The effect of nicotin and tobacco is directly upon the musculature of the circulatory system. Fatty degeneration of the heart from excess tobacco has been demonstrated, and in animals similar changes in the musculature of the heart and vessels have been noted. There is besides this an increase of blood pressure during the nicotin intoxication, which may also have a bearing on the disease process.

We may say, therefore, that the untoward effect of nicotin and tobacco on the arterial system appears quite definite, but that definite evidence is lacking that alcohol and lead produce arteriosclerosis.

That adrenalin, barium chloride, hydrastin, digitalin and other poisons have degenerative effects on the musculature of the arteries, has been shown in animal experiments, but what bearing these observations have on toxic arteriosclerosis in man remains undecided.

3. *Work.*—We can, however, present a much stronger case that work produces arteriosclerosis. Evidence has been accumulating for many years, but more particularly in the last decade, that an excessive amount of work thrown on the arteries will lead to degenerative changes. The musculature of the vessel wall is subject to fatigue like other muscle fibres, and this fatigue results in the first place in a loss of tone and dilatation of the arterial tube, while if the strain be continued the muscle fibres are lowered in their vitality. This loss of vitality is evident in the microscopic "cloudiness," and a deposit of fat granules in the substance of the muscle fibres. From this condition the degeneration progresses, until finally the death of the muscle elements leaves a much weak-

ened arterial wall. The commonest site of these progressive degenerations of the media is found in the femoral artery. Such individuals whose occupation requires them to be constantly on their feet show the various stages of degeneration and loss of the muscle elements of the media, accompanied by multiple aneurysmal sacs. These aneurysms vary in size from a bead to that of a marble.

In a similar manner the radial, tibial, popliteal, iliac, uterine and brachial arteries show degenerative changes, and occasionally aneurysms, as the result of the intermittent increased blood pressure within them.

Thayer and Fabyan examined the radial and other arteries from a series of cases which during life had been studied in the wards of the Johns-Hopkins Hospital. The authors found that wherever arteries had been subjected to strain, these vessels showed scleroses, due either to the extra tissue by which the vessels had fortified themselves, or to degenerative processes in the media (calcification). These authors state that "an unduly thickened radial at an early age may mean one of two things: (1) the vessel has been subjected to unusual and exceptional strain or (2) it is a vessel which, from inherent weakness, has been unable to cope with conditions which might ordinarily be regarded as normal."

The truth of these inferences respecting the effect of excessive work on the arterial walls has been demonstrated experimentally, as I have already reported.

In all these instances of work arteriosclerosis there has been an external influence which has caused the high blood pressure in the arteries. The constant tramp of the pedestrian continually jars and jogs the blood column in the vessels of the legs, which is only relieved by the elasticity of the media. The daily use of the right arm in manual labor, and more particularly in such work which throws the blood suddenly backward and forward (as in blacksmithing) leads to hypertrophy and later scleroses of the radial and brachial arteries. It is, however, more difficult to gauge the effect of mental labor on the vessels of the brain. That there is an increased flow of blood to the brain during mental activity is known, but we lack in this the jarring of the blood stream on the vessel walls. However, long continued mental strain with a recurring high pressure is probably also able to completely tire the muscle fibres with, in extreme cases, resulting degenerative changes in them. The same is likely true of the arteries of other overworked organs.

4. *Old Age.*—It is perhaps improper to classify old age among the agents bringing about a diseased condition of any organ, but what we wish to imply is that the continuous wear and tear of the system, even that amount which takes place under physiological conditions, does after a certain length of time leave its mark upon the tissues. The French have spoken of this normal wear and tear as "the rust of life." In almost all organs the senile changes amount to disturbance of nutrition with its consequences. Simple atrophy of the organs is the earliest sign of senile changes, and in the arteries this amounts to a diminution of the media. Death of cells need not necessarily be present in simple atrophy, but as soon as this does result there is a simultaneous increase in the connective tissues. This increase in connective tissue may only be relative, but is frequently real. The senile type of arteriosclerosis in vessels of the elastic tissue type is very definite and is not to be mistaken for any of the other forms. Its mode of selecting that part of the media which is most poorly nourished is characteristic. I cannot agree with Romberg's designation of arteriosclerosis in general, as an "abnutzungs krankheit." It has been definitely shown that there are certain agents which bring about arteriosclerosis of particular kinds, and when these agents are infections, fevers or intoxications, it would be wrong to speak of the arterial lesions as processes of wear and tear. The term "abnutzungs krankheit" as regards arteriosclerosis is only applicable to that type occurring in old age, and as this type presents such characteristic features from the usual arteriosclerosis, I would well recommend Romberg's term for this disease.

It has been well established by Aschoff that the elastic fibres of an artery undergo a change with advancing age. There is a definite increase in the quantity of elastic tissue from infancy to adult life, and this increase appears to be in direct proportion to the increase of pressure within the arteries. However, our knowledge of the variation of the blood pressure at the various ages of life and in the different blood vessels is imperfect; and until this is determined definite statements cannot be made for any particular artery. Aschoff takes it, however, that for every continuous increase of the arterial tension there is a parallel development of elastic fibres. This physiological development of elastic fibres is common to all persons up to middle age. From this time on the senile changes in the arteries creep in, and we can no longer follow the changes in individual tissues, common to all persons. Aschoff finds that there is a senile arteriosclerosis localized to the intima which consists of thickenings and degenerations particularly noted at the points of bifurcation. As, however, these changes are not constant in every person over middle age, and as in some cases of old age these intimal degenerations are completely lacking, I am reluctant to regard these as senile arteriosclerosis. Rather than being only the result of wear and tear, I believe these plaques at the points of division of the arteries represent lesions of definite etiological factors and not senility. It is otherwise with the degenerations of the media which I have above described as senile arteriosclerosis. These granular, fatty and calcareous degenerations of the muscle cells, I have found only in senility in human arteries, and have noted that in all cases of old age these degenerations are to be found.

Interesting observations were made by Foster in our laboratory, on the changes taking place in the elastic tissue of the aorta in advancing age. Foster found that there were definite periods in life when these changes occurred. The elastic fibres of the media show a gradual increase in their size and number up to the thirty-fifth year. With this increase in the elastic tissue, the relative proportion of elastic fibres to muscle tissues is altered in favor of the elastic laminæ. After the thirty-fifth year there is a period of quiesence lasting for about fifteen years. During this time no definite changes occur in the elastic fibres save when some intercurrent disease processes develop in the vascular tissues. The third period of life,—from about the fiftieth year onward, is marked by the atrophic changes of senescence. The muscle fibres atrophy more rapidly than the other tissue cells, leading to a relative sclerosis, and an apparent increase in the elastic fibres. Moreover the elastic tissue in itself shows the changes of the decay of life. The fibres no longer possess the elasticity of the adolescent structures, the staining reactions are no longer uniform and the individual fibres show rough and ragged borders in place of the smooth undulating contour of the young fibres. The aortic wall in this third period may be thinner than is usually seen in the second period, due to the actual loss of muscle strands and lamellæ, with the close crowding of the elastic rings.

It is to be observed that in the vessels of old age the relative increase in the elastic tissue of the artery, even in the absence of an actual connective tissue increase, leads to a less elastic wall. The two factors, loss of muscle tissue and alteration in the nature of the elastic fibres, are responsible for this.

ANEURYSMS AND MEDIAL DISEASES.

A brief reference must be made of the association of medial diseases with aneurysms.

Although there have been a great number of reports in the literature concerning aneurysm, there is to the present day no common opinion concerning their etiology. On the contrary, like arteriosclerosis, the views expressed on the subject of aneurysms have been so divergent and manifold that difficulty is experienced in following the history of this subject, and of giving proper credit to the observations of the older writers.

To Vesalius we are indebted for the first recognition of aneurysm, but little information is obtained of their nature from his descriptions. His contemporary, Fernelius, offered the first explanation for the condition, which was accepted for the time. He taught that every aneurysm consisted of a dilatation of all the arterial coats, and that syphilis was the cause. It was soon found that his definition was too narrow, and a division was made into true and false aneurysms.

Various descriptions of aneurysm of different arteries are to be found in the writings of the masters of the early eighteenth century (Morgagni, Severinus, Guattani, Verbrugge, Lancisi). By true aneurysm Lancisi referred to those conditions in which the arterial wall was weakened and dilated, while a false aneurysm was a dilated artery as the result of external injury. Interesting it is too, that these observers recognized an association of syphilis to aneurysm, but expressed an opinion that possibly it was the mercurial treatment and not syphilis which acted upon the vessels.

It will be appreciated that the observations made upon the appearance of aneurysm, were isolated to the cases coming into the anatomist's hands. Commendable are, too, the accurate macroscopic descriptions which they have handed down to us. On the other hand, the want of knowledge concerning structural changes in the arteries led to much speculation and to many theories.

At the beginning of the nineteenth century Scarpa described aneurysm as a rupture of an artery produced either by trauma or by a " degenerazione steatomatosa " or through ulceration, with an effusion of blood into the surrounding tissues. He further classified these lesions, " spontaneous " when the aneurysm had resulted from disease in the wall, while all the traumatic aneurysms of the arteries he called " spurious." Scarpa has the distinction however of first stating that no aneurysms arise without a disease or abnormal condition of the media. Monro, on the other hand, claimed that the term aneurysm was applied to localized or diffuse stretching of all of the arterial coats, while false aneurysm referred to the blood sac formed outside of the artery but still in communication with the arterial channel.

Scarpa in 1804, pointed out that dilatations of the arteries were associated with a peculiar and distinct disease of their walls, but not until 1815 was it shown by Krisig and also Hodgson that these arterial diseases were of an inflammatory nature. More particularly was it shown by Krisig that this inflammation was present in almost every form of aneurysm and that possible ulcerations were secondary processes in the condition. A series of observations were then reported by Bruns, Guthrie, Lobstein, Donders and Jansen, most of whom supported the inflammatory origin of aneurysm. Guthrie laid stress upon chronic irritation or inflammation as the factors leading to alterations in the arteries. " The first and simplest change," he says, " is a loss of the elasticity natural to them, which may lead to a state of dilatation without abrasion or rupture of any of the component parts of the artery, although sometimes accompanied by a general diminution of substance of the middle coat." Guthrie studied many of the specimens collected by Hunter, and it is of interest that he recognized a primary disease occurring in the media having no relation to changes taking place in the intima.

Rokitansky on the other hand believed that the mechanical functional overstrain of the arteries was a predisposing factor for endarteritis, and also for the development of aneurysm. He contended that the portion of the aorta which was called upon to do the greatest amount of work showed the development of aneurysm most frequently.

Traube had supported the inflammatory theory of aneurysm and believed that the white blood cells were attracted from the blood stream through the endothelium, and formed there the white sclerotic plaques of intimal thickening. The result of this superficial inflammatory reaction led to a weakening of the wall. Koester agreed with this contention, but thought that the degeneration of the intima was primary and the invasion of leucocytes was a secondary condition.

These theories were strongly opposed by Virchow. In the first place he held that endarteritis was a true inflammation of the intima resulting from a given irritation. Such inflammation could arise from various causes and possibly through the action of the blood upon small erosions in the intima. From his observations Virchow came to recognize differences between lesions resulting from proliferative changes in the intima, and the primary fatty degenerations of this coat. He also differentiated the minute changes occurring in the media either with or without intimal diseases. In these latter states he found that aneurysms were most prone to develop.

Still other views were brought forward. v. Recklinghausen was of the opinion that the primary disease preceding aneurysm was a mechanical overdistension of the vessel leading to rupture of the elastic fibres of the vessel coat. Helmstaedter too ascribed the main changes leading to aneurysm as destruction of the media and more particularly the elastic tissue. More direct evidence was soon brought forward by Trompetter and Auerbach that many of the aneurysms of the aorta were associated with a mesarteritis and that in some cases little or no damage was to be found in the intima.

Some years later Koester altered his original view and expressed his opinion that arterial disease was commonly associated with an inflammatory infiltration about the vasa vasorum. Koester in fact now believed that this was an essential condition in arteriosclerosis. Thus we find Koester teaching that every endarteritis had a mesarteritis preceding it. Later on we find Kraft agreeing with but modifying Koester's view. Every inflammation of the arteries, he said, attacked the media and did not advance into the intima. He believed, however, that aneurysms were the result of a diffuse inflammation in the muscular coat which advanced to it from the adventitia by way of its nutrient vessels.

Almost all the authors were agreed on the presence of an antecedent disease, in the arterial coats, to aneurysm, yet these same authors expressed some doubt in the direct relationship of arteriosclerosis to aneurysm. The chief stumbling block lay in the fact that arteriosclerosis was a disease which progressed with advancing years while aneurysm was most frequent between the ages of thirty and forty, and did not increase in frequency in old age. Crisp and Lebert, give very comprehensive tables indicating the frequency of aneurysm at the various periods of life. A similar table is also given by Lisfranc.

Age.	1–10.	10–20.	20–30.	30–40.	40–50.	50–60.	60–70.	70–80.	Cases.
Crisp	1	5	71	198	129	65	25	8	502
Lisfranc	4		17	29	37	17	3	3	120
Lebert	16		42	80	75	70	35	0	318
Lidell	2	8	31	81	69	24	20	6	241
Total	36		161	388	310	176	83	17	1,181

In opposition to these figures, Richter finds that in a series of 366 cases of aneurysms collected by him the age incidence of arteriosclerosis and aneurysm is not so dissimilar.

10–20 years.	20–30.	30–40.	40–50.	50–60.	60–70.	70–80.
5	49	217	269	133	52	11

Peterson-Borstell found that in 2,982 autopsies 64.7 per cent. of the cases between the ages of fifty and eighty had endarteritis, while 95 per cent. of the cases above eighty years showed evidence of the disease.

In the discussion of the relationship of endarteritis to aneurysm Birch-Hirschfeld emphasized the frequency of the former condition after middle life, while aneurysms are relatively few at this age. In this point alone, he says, there is evidence that the ordinary endarteritis is not directly associated with dilatation of the vessel.

Lawson, in England, too recognized the infrequency of aneurysms with atheromatous processes in the arteries. His observations were chiefly among the soldiers at Aldershot, and he says that "aneurysm, as I have met with it among soldiers, seems frequently to exist quite independent of that form of disease of the arteries, and the destruction of large portions, of even the whole three coats may take place by an acute process and without a trace of atheroma in the neighborhood" (Osler). Aneurysm occurs at the Kiel Pathological Laboratory in the frequency of one in two hundred autopsies (Kroeger).

There have been a few cases reported in literature in which aneurysm was noted in the arteries which otherwise appeared quite healthy. It is probable that in these cases the vessel was locally diseased or that minute histological examinations were not undertaken to demonstrate conditions which could not be recognized with the naked eye. Such remarkable specimens, however, led some to support the mechanical theory of aneurysms.

With a development of better technique, many observers have busied themselves in demonstrating one or more causative factors in human aneurysms or in reproducing the lesions in animals.

This brings us to fairly modern times, when the controversy respecting aneurysm became centered about its relation to syphilis. But we must not fail to recognize that the history of syphilitic arterial disease takes us a long way back in the literature. Ambroise Paré, although not the first to observe the occurrence of certain arterial diseases and aneurysms after syphilis, was nevertheless the strongest exponent of their relation, in the middle of the sixteenth century. Similar observations were later made by Lancisi, Severinus, Morgagni and others, who, although observing the relationship of syphilis to aneurysm, did not appear to have decided whether the result was from the French disease or from the mercurial treatment.

For some years little stress was laid upon these findings. Guthrie in 1830, denied the association of syphilis with aneurysm. He recognized the frequency of aneurysm in the ascending arch of the aorta in which he found all the tunics more or less retained. These aneurysms he spoke of as preternatural dilatations. He says, "preternatural dilatations are most frequently met with in the ascending aorta and at the arch; they have been less often observed in the aorta descendens. They are not uncommon in the arteries within the skull." This author makes a distinction between preternatural dilatations " when an artery is enlarged in its whole circumference," and aneurysms " when the tumor seems to grow from one side or part of the artery alone." In aneurysms Guthrie found that the wall of the sac not infrequently showed inflammatory conditions which he believed were due to the action of the poorly circulating blood, in the sac, upon the arterial wall. It is not improbable that Guthrie's preternatural dilatations or fusiform aneurysms were a mild and more diffuse syphilitic lesion of the aorta.

In 1862, Aitken, in England, found among twenty-six cases of syphilis, seventeen aneurysms of the aorta. In 1862, Davidson reported these and other cases in the Army Medical Reports of England. These reports of syphilitic aneurysm were followed by others in England, which, however, are scattered through a rather inaccessible literature.

The frequency of aneurysm in the army was a subject of comment in the middle of the last century. The majority of reported cases of that time came from England, until continental authors spoke of " England, the land of aneurysms " (Spleidt). Billroth in his work on pathology stated that " the occurrence of aneurysm had a remarkable distribution in Europe. In Germany aneurysms are uncommon, as they also are in Belgium, they are more frequent in France and Italy, and most commonly found in England. It is difficult to give definite reasons for this, but it is a fact that arterial diseases along with rheumatism and gout are more frequent in England than in any of the other European countries."

This variation in the incidence of aneurysm in different countries is well illustrated in the statistics collected by Osler. From his figures it is found that at the Johns-Hopkins Hospital, aneurysm is more common than in Germany or even England.

Important observations were made by Francis Welch in 1875. He had the opportunity of studying thirty-four cases of aortic aneurysm, occurring in the army, over half of which had had a definite attack of syphilis. Welch is the first to give us a full account of the appearance of syphilitic lesions in the aorta, and to give the points of differentiation from the other arteriosclerotic processes. He pointed out that where fatty degeneration occurred in a syphilitic aortitis, it was an associated and not a primary lesion.

As Osler points out, it was chiefly the army physicians of England who were convinced of the immense importance of syphilis as the prime factor in aortic aneurysm.

At the time of publication, Welch's contentions received considerable criticism from others than the army medical physicians in England, and the general controversy on the question of the etiology of aneurysm was opened with renewed interest. It may be said that Welch's observations on the appearance and differentiation of syphilitic aortitis are the beginning of a new era in our knowledge of syphilitic disease of the arteries. The fundamental principles enunciated by Welch, associating aneurysm with syphilis, have been little altered today.

In Norway, we find similar controversies respecting the association of syphilis with arterial disease. Heiberg in 1876 pointed out that probably the greater proportion of chronic inflammation of the arteries (? aorta) was the result of syphilis, and his opinions were later supported by his countrymen Malmsten and Rasch. In France, too, little support was given to these new views. However, in 1879, Vallin reported a case of aortic aneurysm following a definite attack of syphilis, and these observations were soon followed by many others. A similar scepticism prevailed in Germany, until the clinicians, Gehardt, Quincke, Fraenkel, and others, observed the association of these diseases in their patients. The German pathologists at first gave but a passive affirmation to these findings, but later when more acute attention was directed to the subject it was demonstrated that a more than casual relationship existed between syphilis and aneurysm.

To Heller and his pupils we owe the greatest indebtedness for the definite differentiation of aortitis syphilitica from chronic endarteritis. Since Heller first, through his pupil Doehle, directed attention to the importance of syphilitic aortitis, he has repeatedly brought to our notice cases of aneurysm associated with syphilis of the aorta. The collected reports from the Kiel school give very complete information respecting the frequency, site and syphilitic nature of aneurysms.

Recklinghausen believed that aneurysm of the aorta developed as a result of a primary rupture of the elastic fibres. This process was more fully described by his pupil Helmstaedter, who found in several cases of aneurysm of the aorta, in which the intima was comparatively normal but in places retracted, that peculiar areas occurred in the media in which the elastic fibres had disappeared or appeared to have ruptured. Into these areas of destruction a new connective tissue developed but formed a weaker wall than normal.

One cannot but be struck by the similarity of the descriptions of Helmstaedter with the picture of syphilitic mesarteritis.

Heubner was one of the early investigators who indicated that syphilis of the arteries was of a specific nature. From his studies, however, he was led to conclude that the disease began in the endothelium and that the media and adventitia were only later involved.

Chiari too points out the points of differentiation between the ordinary sclerotic processes in the aorta, and those of syphilis. The latter, he said, formed a class of chronic mesarteritis which was distinct and could be separated from other forms of chronic mesaortitis. His work has shown that syphilis of the aorta is a destructive disease of the media which advances to it from the adventitia.

It is worthy of note that there have been not a few cases of aneurysm reported associated with tabes dorsalis (Berger and Rosenbach, Euslin, Molt, Halpern and others).

In the statistics on the association of syphilis and aneurysm there are some interesting data. Heller pointed out that he had found syphilitic aortitis in cases where syphilis was otherwise not recognizable in the body, while on the other hand, he found that some individuals who had had definite and severe attacks of syphilis, had not shown any recognizable changes in the arteries. Thus the occurrence of the arterial changes in syphilis varies considerably. Aitken found aortic changes in 68 per cent. of syphilitics; Welch found syphilitic disease of the aorta in 46.1 per cent., while Henderson demonstrated lues in 62.5 per cent. of aortic aneurysms. The history of the individual cases of aneurysm is also interesting in that the reports indicate that aneurysm may develop from one (Moore) to thirty-three (Malecot) years after the infection.

The distribution of aneurysm of the aorta follows the frequency of syphilis in the various parts of this artery. Thus as it has been repeatedly shown that syphilis has a predilection for the ascending limb and arch of the aorta so aneurysm too is more frequent in these portions. Of forty-eight aortic aneurysms examined at the Pathological Institute at Kiel (from 1872 to 1899), thirty-eight were males and ten females. The average age was 52 years, the youngest being 25, the oldest 83 years. The greater number, 27, occurred in the ascending aorta, 11 in the descending, 10 in the arch. In one case an aneurysm was present both in the ascending and in the descending aorta (Kroeger).

If we now sum up the points associating syphilis with aneurysm, we find that syphilis is prone to attack the ascending aorta by a mesarteritis whose prime feature is a destruction of the essential tissues of this coat. The fibrosis in the wall along with the not unusual extensive endarteritis are secondary processes. With the media destroyed the artery is much weakened leading to dilatations of various degrees, or even rupture.

It is only with the appreciation that the media is the mainstay of an artery, that the full bearing of the importance of syphilitic arteritis is seen. Today we lay it down as a law that *aneurysms can only result when the media is weakened,* and do not result from any disease process isolated to the intima or adventitia. Hence, too, it at once becomes evident how important are the diseases of the media.

In discussing the question of aneurysm in general we must recognize the occurrence of arterial dilatations from causes other than syphilis. The greater frequency of syphilitic aneurysm in the aorta serves as no guide to the number of cases of aneurysm due to syphilis in the other arteries. The peripheral arterial system is much more exposed to direct injuries which damage and weaken the arterial wall, so that aneurysm results, than the aorta. Gunshot and stab wounds are among the more common of these injuries. Saigo reports the occurrence of many traumatic aneurysms during the Russian-Japanese War, and he believes that their great frequency was the result of modern ammunition. These aneurysms developed from two to five weeks after the injury and were commonest in the upper arm and thigh.

Again, as we have pointed out above, of the ordinary sclerotic processes arising in the arterial system the medial scleroses are in much greater proportion in the peripheral vessels than in the aorta, and further these medial scleroses of the peripheral system are more common than the affections of the intima of the same vessels. Moreover it is to be noted that these medial scleroses develop from varied causes and are to be found of different grades of intensity in all individuals over fifty years. We would not be surprised therefore, to find aneurysmal pouchings in the peripheral arteries in many individuals beyond middle life. In my own experience this has been a common finding when looked for. Particularly easy is its demonstration in the femoral and iliac arteries where transverse pouches and sacculations are so often present. Often these pouches appear multiple, and lie in parallel rows across the artery. As I have indicated elsewhere, these pouches are not so prominent during life when the blood pressure obliterates the still elastic and less involved ridges between these aneurysms. It is to be appreciated that during the development of these small sacculations the degenerating media becomes sclerosed and calcified so that the pouch forms a small rigid cavity, fully dilated by the blood pressure. After death with the release of the internal pressure the more healthy portions of arterial wall around the sac contract, exaggerating the depth of the cavity.

Although the frequency of peripheral aneurysms of the extremities is relatively great, their importance is very much less than that of the aorta. The former are as a rule self limited and do not progress beyond the shallow cuppings of the wall. On an average the peripheral aneurysmal pouches are present in one out of every three individuals over fifty years. Although these aneurysms of the peripheral arteries are most often found in the vessels of the extremities, they are also observed in the splenic, mesenteric, vertebral and cerebral arteries.

Another type of arterial disease leading to aneurysm must be noted. Endarteritis chronica deformans with atheroma developing in a small artery has a much greater significance for the development of aneurysm in the small arteries than in the aorta. It is not so many years since pathologists expressed the view that aortic aneurysms were commonly the result of endarteritis (Virchow, Rindfleisch, Foerster and others). This today we can support only for a particular group of vessels.

It has been shown above that the frequency of aortic aneurysm occurs between the ages of thirty to fifty, while the development of endarteritis increases from this age onward. It is to be assumed, therefore, that in the aorta, endarteritis has less significance in the production of aneurysm than other causes.

We are familiar with the nodular atheromatous processes occurring in the cerebral and coronary arteries, and we are frequently astounded at the enormous pearly plaques that develop in these vessels, almost bringing about occlusion of the lumen. A similar sized plaque in the aorta would cause little interference or injury. In the small arteries, however, degenerative changes of atheromatous softening develop beneath the endothelial overgrowth. This atheroma is not confined to the intima but at times also invades the media, which if deeply involved weakens the staying power of the wall. At other times the endarteritic plaque does not itself enter the media, but by its growth presses upon the tissues to such a degree that the coat is thinned and weakened. This pressure atrophy of the media does allow some giving away of the artery with an irregular outline of its lumen. It is a common observation that the endarteritic plaque rests very loosely upon the underlying media, so loosely, in fact, that it falls out during cutting. These small arteries with extensive chronic endarteritis form tortuous and irregular cylinders, in whose walls aneurysmal pouches are evident. These lesions are not of syphilitic origin and are, at times, seen in a single system of vessels (cerebral, coronary, mesenteric), while the aorta is little or not at all involved.

Richter was positive that hard manual work which was one of the causes of arteriosclerosis was also the most important factor in aneurysm. According to him, aneurysm and particularly of the aorta was a disease associated with the working class, and was directly related to excessive muscular activity. It is undoubted that muscular exertion leads to a greater work on the part of the arterial system, and it has been shown, that in as far as the human peripheral arteries are concerned, a sclerosis develops in the media of these vessels; that endarteritis develops in association with hard work also seems undoubted, but the process is probably one secondary to fatty degeneration of the deeper intima, particularly the musculo-elastic layer.

Goetz believed that for aneurysms, other than those that developed from acute infections, atheroma was an important factor. Manning, v. Leyden and Klemperer held similar views but thought that for the development of aneurysm from an atheromatous process, a trauma in the nature of a severe blow or concussion must accompany it.

In 1898, Manning reported four cases of aneurysm of the aorta which he believed were of endarteritic origin. Two of these were saccular aneurysms, in the ascending aorta, one was fusiform and in the descending aorta, and the fourth was a dissecting aneurysm. From his descriptions of the first two cases and with our present day knowledge of aneurysms, we are inclined to suspect these were associated with a syphilitic process.

Koester was a strong opponent to the view that aneurysm of the aorta developed in consequence to endarteritis. In the development of aneurysm of the aorta there need not be a progressive degeneration of the arterial wall, for aneurysms occur in areas of fibrosis of a former medial destruction. In syphilitic mesaortitis the process is one of chronic inflammation in which the loss of medial tissues is to some extent replaced, step by step, by new fibrous tissue. Although this new tissue is reparative in character, it is far from being a tissue of the same elasticity and strength as the normal arterial wall. With each pulsation, brought to bear upon this scar tissue, there is a slight giving way in the connective tissue fibres, which if there is not a sufficient quantity of muscular and elastic tissue to restore the original length, remain permanently stretched. This yielding of the connective tissue areas in the arteries leads to the production of aneurysms.

This too accounts for the frequency of aneurysm in those cases of syphilitic mesarteritis, where the arterial wall is actually thickened by scar tissue.

It has been shown by Poletebnow that the arterial wall when sclerosed becomes less elastic and at the same time more resistant to a given tension. Examining two strips of aorta each 7.5 cm. long, and taken, one from a young and healthy individual, the other from a much sclerosed artery, he found that the former allowed a stretching to 16.5 cm. while the diseased vessel only lengthened to 9.9 cm. by a weight of 1000 grams.

Similar experiments were carried out by O. Israel, who used strips of aorta 5 cm. long and 5 mm. wide with a constant weight of 75 grams. The aortic strip of an alcoholic lengthened to 6.03 cm.; a nephritic to 6.471 cm.; a normal adult to 6.95; and of a chlorotic individual to 7.422 cm. From his observations he concluded that the arteries lose in their elasticity with advancing arteriosclerosis.

Luck, a pupil of Thoma, observed that at the beginning of the arteriosclerotic process the artery was more readily dilated, while as the process advanced the arterial walls became rigid and did not react as readily to varying pressures. This primary weakening of the artery is a result of nutritional disturbances, which gives evidence of undue stretching before microscopic changes are evident. Similar results were obtained by Lunz who demonstrated experimentally that phosphorus, lead and mercury intoxications reduced the resisting powers of the arterial wall.

These results find full agreement with our own observations, and have their explanation in the altered condition of the media. We cannot however apply the facts of these experiments directly to the question of aneurysm. Namely in demonstrating the lessened elasticity of the aortic wall in arteriosclerosis, as Polotebnow and Israel have done, we are not demonstrating a condition of greater strength or resistance to intermittent pressure and pulsations. If we have in such a sclerotic artery a greater abundance of fibrous tissue, this tissue will be less elastic than a normal vessel, but on the very fact of its diminished elasticity this tissue when stretched, no matter how little, does not return to its original length. Its very condition of lessened elasticity favors aneurysm or at least diffuse dilatation.

Not alone is this true for fibroses of the arterial wall. Any conditions which tend to set aside the inherent elastic powers of the muscle fibres and elastic tissue will at the same time favor the process of dilatation of this vessel. Manchot, Weisermann and Newmann Helmstaedter, Zwingmann and others believed that the early histological changes to be observed in arteries with less elasticity were fragmentation and alteration in the staining qualities of the elastic fibres.

It is not an uncommon finding at autopsy, that the aorta of aged persons, with little or no intimal sclerosis, is thin and dilated. Such vessels owe their thinning to the atrophied media in which both muscle and elastic fibres take part. These arteries are less elastic than those of young adults, but the lumen is more or less uniformly enlarged. These dilatations do not merit the term aneurysm but constitute diffuse ectases of the aorta.

Among the rarer forms of aneurysm is that type first described by Laennec in 1826 as "dissecting aneurysm." This form consists of a rupture of the inner surface of an artery, into the media, while the blood there burrows a sac between the layers of this tunic, and the outer coats remain intact. Some controversy had arisen concerning the exact position which was commonly taken by dissecting aneurysms in the arterial wall. Pennock in 1839 gave an excellent report of a specimen in which he found that the dissecting blood had invaded and separated the layers of the media. This is now accepted, and it is found that the commonest line of separation is between the middle and outer thirds of this coat. The line of separation does not lie between the adventitia and media as was formerly supposed.

Most of the text books, Orth, Ziegler, Kaufmann and others, state that the line of division in dissecting aneurysms is produced by the inflowing blood. This is denied by some. It is admitted by most, and this is obtained from the clinical history, that the direct cause of the tear in the inner coat of the artery is brought on by trauma. However, several cases have been reported in which a granulation tissue was found immediately about the dissecting aneurysm. In these cases it was considered that this inflammatory change in the arterial coat had preceded development of the aneurysm. It is found, however, that some of these cases had lived some time after the exciting trauma, and the possibility remains that the inflammatory change was a secondary development. Such a case is reported by Recklinghausen. Another case of this kind is reported by Babes and Mironescu. They found, that not only was there an inflammatory infiltration close to the dissecting aneurysm (which was of at least two days standing), but that the media of the aorta showed an unusual tendency to separate into two layers in its outer part. Microscopically, this vessel showed small spaces, which the authors consider as potential factors of dissecting aneurysm. This antecedent condition they describe as dissecting arteritis.

Dissecting aneurysms are usually of sudden and rapid onset. They occur most commonly between the ages of fifty-five and sixty-five—more occur after the age of fifty-five than before, an age when more or less aortic medial sclerosis is present. As Professor Adami points out, the condition is not developed in youth or early adult life, and there is an etiological relationship between age and incidence. Further, Adami clearly indicates that dissecting aneurysm is not a development from extensive atheroma. The greater majority of the reported cases showed some nodular but smooth thickening of the intima, but evidence of atheromatous ulceration and calcification was wanting. This is an interesting observation which illustrates that the atheromatous processes in the deep intima and inner media are local disturbances which may erode into the vessel lumen and then exist as passive pathological processes, the outer wall of the vessel being strong enough to withstand the blood pressure.

Although syphilis plays the important role in the etiology of the majority of aortic aneurysms, it appears to be little associated with dissecting aneurysms. The syphilitic aortitis is as we have repeatedly said a chronic progressive inflammation, which shows degenerative processes accompanied by the formation of scar tissue. Media is mainly destroyed, and it is the media and adventitia which develop the enormous interlacing fibrous tissue. These criss-cross bundles of fibrous strands can be stretched and lead to dilatations, but a rent in the inner wall will not burrow in this tangled fibrous tissue. Erosion or rupture of the thinned walls of a syphilitic aneurysm may occur and cause a fatal hæmorrhage, but do not lead to dissecting aneurysm.

In 1896, Adami collected about two hundred cases of dissecting aneurysms from the literature and since this time about forty more have been added. The early reports of Peacock, in which eighty cases are recorded, form an excellent study of the disease.

Bostroem believed that dissecting aneurysm was due to severe strain and trauma. With Adami and others we must agree that severe strain has not infrequently been the exciting cause, but we must also recognize the presence of an antecedent diseased artery.

Dissecting aneurysms follow the same rule which we have indicated for aneurysms in general, " there must be a diseased media." Now we have also pointed out that those conditions in which either an acute mesarteritis or a chronic productive mesarteritis is present lead to aneurysmal dilatations, a condition in which the walls are stretched but not actually ruptured by the internal blood pressure. Again it is to be noted that when an acute inflammatory mesarteritis is further accompanied by sudden strain, a tear occurs in the unaffected intima which leads to fatal hemorrhage through the diseased media and adventitia (myocotic aneurysms).

On the other hand in dissecting aneurysms we are dealing with individuals over middle age, who, whether they show a nodular endarteritis or not, have definite degenerative changes unaccompanied by a productive sclerosis in the media. This form of disease is of the nature of the true senile arteriosclerosis previously described. The media is atrophied, the muscle cells are small and in part lost, the elastic fibres are coarse and have lost much of their elasticity. Although the vessel wall possesses senile degenerative changes true aneurysms do not develop, the tissues still being able to withstand normal pressure. When however the vessel wall also suffers a severe strain (lifting heavy weight, straining at stool, a fall), the intima may be ruptured by knife-like cuts. These intimal tears also include and enter the upper media so that the blood gains entrance into the middle of the media where the blood pressure separates the lamellæ between the middle and outer third. The course of least resistance is parallel to the long axis of the artery, as the majority of muscular fibres are disposed circularly while the elastic fibres form a system of perforated tubes encircling the artery. The fairly healthy adventitia also prevents the escape of the blood into the surrounding tissues.

As with all types of arteriosclerosis the extent of the disease process varies in all individuals, so too the severity of degenerative medial arteriosclerosis varies much in individuals over fifty years of age, and determines the potential danger of dissecting aneurysms when coupled with trauma or strain.

There is another type of aneurysm of the peripheral arteries which forms a class quite by itself. These are the small sacculations which develop in association with periarteritis nodosa. It will be unnecessary to again review the nature and history of this rare disease, which we have discussed in a previous chapter. The points, however, which are of particular interest at this point, are the development of multiple aneurysms—numerous in some specimens, rare in others. The pathological changes found by the various authors are remarkably constant, and the appearance is characteristic. The nodules develop on the medium-sized arteries of the abdomen, heart or parenchymatous organs and are composed either of solid tissue masses, aneurysms, or organized thrombi within saccular dilatations. In all instances localized degenerative features are to be found in the media or in the adventitia and media, while an inflammatory reaction is present in the immediate neighborhood. In a few cases the arteries, although showing the nodules, have had no true aneurysms.

Whatever be the etiological factor or factors in this disease, focal necrosis or degeneration of the arterial coats is an important primary feature. This may or may not be accompanied from the first by an inflammatory reaction, and on the presence or absence of this reparative inflammation depends the development of aneurysm. In those cases where the destruction of tissue is marked before repair takes place, small sacculations develop in focal areas. In others again the degeneration is accompanied by a lively repair which builds a mass of granulation tissue on the outer side of the media and in the adventitia, so that the artery does not yield under its normal pressure.

Although the etiology of this disease is still in doubt, the development of aneurysm follows the same rule as has been indicated for other dilatations above—namely a destruction of the medial tissues.

By some the disease has been associated with syphilis, and although Verse has found spirochætæ in two cases of gummatous periarteritis he was unable to find these organisms in the nodules of true periarteritis nodosa. It would probably be well to subdivide the cases of nodular periarteritis into those of syphilitic origin and those whose etiology to-day remains uncertain. The lesions of the latter class are often quite acute.

Still another type of aneurysm of the large arteries has been described associated with acute infections and more particularly with infective endocarditis. Acute infections of the aorta are remarkably rare, but when present have serious consequences. Ponfick was the first to describe the acute vascular changes occurring in "embolic aneurysm," associated with endocarditis. He found this condition at the bifurcation of an artery, and believed that the aneurysm was the result of the localized embolus. Hochhaus described a case of advancing infection from the aortic valves which led to aneurysm. The verrucose process extended into the large vessels and along the ductus arteriosus to the pulmonary artery. Eppinger described a series of cases in which aneurysm of the aorta had developed following an acute infection. Eppinger differed from Ponfick's view in that he believed that these aneurysms developed in consequence of an acute septic inflammation of the media. Microorganisms were demonstrated in the damaged tissue of the artery and in the thrombotic mass when present. These aortic lesions were spoken of as mycotic aneurysms. Schroetter recognized the same disease under the name thromboarteritis suppurativa. In England, Church and Langton and Bowlby believed that such aneurysms developed from localized emboli which caused nutritional changes in the arterial wall, in the nature of an infarct.

There are certain characteristics of these unusual aneurysms which are constant. They occur most commonly in the ascending limb of the aorta, are frequently multiple and show acute inflammatory conditions in the media. From the intimal surface they have characteristic linear or stellate knife-like tears in the intima which lead either into the tissues of the media producing a dissecting aneurysm, or perforate the entire wall with fatal hemorrhage. Their onset or development is usually sudden.

Thoma, who opposed Eppinger, took an intermediate stand between the mechanical and inflammatory theories of these aneurysms. He held that he could demonstrate an abnormal elasticity in the media of these vessels, due to atrophy which was the basal feature he believed underlying all aneurysms.

Richter has described seven such cases observed in Heller's laboratory. The lesions were in the aorta and associated with endocarditis. Theile also reported a case with a four-cornered rupture in the ascending aorta, and associated with acute mitral and aortic endocarditis. McCrae recently reported another case with multiple lesions in the ascending aorta.

Mycotic aneurysm, therefore, results from a type of acute mesarteritis, probably arising from an infection entering the media by the nutrient vessels. In several cases the bacteria have been demonstrated in the lesion.

In a word we may dispense with the discussion of aneurysms experimentally produced. The earlier investigators obtained in their experiments of mechanical injury to the arteries, dilatation either diffuse or local at the point of damage. Arteries which were crushed or which had a portion of the outer coats excised gave way, sometimes by rupture, at other times in saccular ballooning. This is what one would expect and adds no new information to the observations made upon injured arteries in the human subject. By the method of excision it is possible to determine exactly how much of the external tissues must be lost before the normal pressure produced a dilatation. It is to be remembered that the strength of the coats of a vessel is dependent upon the artery affected, and upon the health of these tissues. So, whereas in a normal vessel, the intima and one third of the media can support the blood pressure natural to that vessel, a vessel with "diseased" tissues will not be able to do so.

The later experiments with various toxins and drugs which act upon the media of arteries have clearly shown how intimately medial scleroses are associated with aneurysm. Many of these drugs produce degenerative lesions confined to the media alone and many of these vessels exhibit aneurysms, varying in size dependent upon the extent of the tissue involved. Saccular and fusiform aneurysms are most readily produced, and B. Fischer reports the production of a dissecting aneurysm in the aorta. In no instance was aneurysm ever produced without definite changes in the media, while at the same time aneurysm often occurred in the absence of disease in either the intima or adventitia.

Experimentally aneurysms have also been produced by mechanically and intermittently raising the blood pressure. Such aneurysms have been explained as dilatations resulting from overstrain and fatigue of the elements of the media.

Process Underlying the Various Forms of Aneurysm.—It is not our intention to repeat the discussion concerning the different kinds of aneurysm, but to point out that each type of aneurysm in the accepted classification has its underlying cause which conforms with one of the types of the diseases of the media, as we have arranged them. From this standpoint we are able to more readily appreciate the processes at work in the production of aneurysm, and at the same time develop a classification which is common to medial scleroses and aneurysms respectively.

Granted that we are agreed in the all importance of medial disease for the production of aneurysm, we may adopt the same subdivisions above indicated for medial diseases.

The main classes, (I) productive or inflammatory lesions and (II) degenerative lesions, may be adopted for the classification of aneurysms.

Using these basal divisions we find that in Class I, there is a type of aneurysm (mycotic) associated with an acute infective mesarteritis; while another type, multiple nodular aneurysms, are associated with the unusual disease, periarteritis nodosa.

As we have seen severe chronic productive or inflammatory processes in the media are mostly of syphilitic origin and give rise to saccular aneurysms of the aorta. That type of chronic productive mesarteritis which is secondary to chronic endarteritis, Chiari's

Type A, gives rise to the sporadic aneurysms in the peripheral arteries, most often seen in the coronary and cerebral arteries, and rarely if ever to saccular aneurysm of the aorta.

Of the second class of medial diseases, the degenerative changes, there are several types which are the forerunners of aneurysm. Simple atrophy of the media, and particularly that of old age leads to slight and diffuse ectases, more commonly observed in the aorta.

Senile arteriosclerosis of the media of the aorta in which fibroses are not evident, when coupled with strain or trauma is the factor of greatest importance in dissecting aneurysm.

Medial scleroses of the peripheral arteries, which we have referred to as Moenckeberg's type, are directly associated with, and the precursors of the multiple pouchings which are found in the vessels of the extremities and less frequently in the vessels of the abdomen.

By experimental means we have been able by the use of certain drugs and also by the intermittent increase of the blood pressure to produce fusiform aneurysms and pouchings of the arterial coat. In these instances the media showed degenerative changes like those found in the Moenckeberg type.

It is seen therefore that the different types and situations of aneurysms have their reason in the nature of the medial disease which precedes them; and that the medial disease is in part dependent upon the artery affected.

SUMMARY.

The media is the mainstay of an artery, and upon its integrity depends the resisting power against intravascular pressure. It is evident that the media is a very important, if not the most important structure of an artery to carry out its proper function, and it follows that the disease processes attacking the media, hold a very important place in the general discussion of arteriosclerosis. The very fact that some type of medial disease underlies every kind of aneurysm, puts this type of arterial lesion among the most important to command our attention.

We have adopted the general term medial arteriosclerosis for all those conditions in the arteries, in which the process in the media is responsible for the hardening of the arterial wall. We have moreover also discussed under this designation the acute stages of the diseases which, when in their process of healing, lead to the true clinical scleroses. It is fallacious to attempt the discussion of any sclerosis without considering the acute stage of the disease, if such was present.

To all types of medial disease of the arteries the term atherosclerosis (Marchand) is inapplicable. The coining of this term was to give a clearer word picture of the combined atheromatous and sclerotic processes in the intima. True atheroma does not occur in the media save as an extension of the process from the intima. There are, however, many sclerotic processes in the media, for the whole of which the designation of medial arteriosclerosis seems the best. The addition of new terms to an old and well recognized disease can only lead to confusion, and until certain definite types of disease can be segregated from the general one, it is best to leave the nomenclature undisturbed. There is to-day at least one type of medial arteriosclerosis which merits special recognition and that is syphilitic mesarteritis; to this there possibly might be added a second, Moenckeberg's arteriosclerosis, a degenerative condition of the media following intermittent arterial overstrain.

For the ready comprehension of medial arteriosclerosis I believe that the subdivisions as are given above will prove an aid. Specific names are not suggested for any of these classes, for the distinct purpose of retaining the general class name of medial arteriosclerosis for all, and naming the types by their pathological characters. I have also avoided speaking of the different types of medial arteriosclerosis by the names of their etiological factors, as it is impossible to distinguish those types in this manner. The infectious and the toxic types have under certain circumstances identical appearances, and these in turn have some resemblance to "work" arteriosclerosis. Hence it seems to me that we can do no better than to group the varieties of medial arteriosclerosis according to their pathological processes. In our arrangement of these diseases there are two main classes of medial arteriosclerosis, (I) the productive and (II) the degenerative type. The former can be subdivided into three, the latter into seven groups according to the character of the lesions (see page 17).

In suggesting this classification of the medial diseases of the arteries we fully appreciate the difficulties and the arguments which may be brought against it. Primarily, we cannot deny the frequency with which productive lesions are associated with degenerative ones, but when the given specimen is closely studied it is possible to determine the nature of the primary and most important lesion. Some types of productive arterial changes are prone to be followed by degenerations, while on the other hand degenerative processes are often accompanied by or stimulate productive fibroses. But in classifying an arterial lesion we must consider not only the most apparent condition then present, but also the process bringing it about.

The principal factors leading to medial arterial disease are: (1) Infections, (2) poisons, (3) work and (4) old age (physiological wear and tear). The effect of any one of these factors upon the arteries is dependent upon the histological structure of that artery and also upon its function. The same agent may give rise to several kinds of arteriosclerotic processes, but the presence of arterial disease in one system of vessels does not indicate disease in another arterial system. Medial sclerosis is often present in the absence of intimal arteriosclerosis in the same vessel.

In different stages of its course, medial arteriosclerosis alters its character, so that at different times it would be differently classified.

Aneurysms are directly dependent upon the diseases of the media of arteries, and the nature of the aneurysm is determined by the character of the disease in the media. The different forms of aneurysm can be classified along with the particular medial diseases, as is indicated in the previous chapter.

Syphilis is the most important factor leading to chronic mesarteritis and aneurysm of the aorta. On the other hand, medial weakenings from causes other than syphilis are more frequently associated with aneurysms of the peripheral arteries. Taken all in all, the aneurysms of the peripheral arteries are more common than aneurysms of the aorta. In the peripheral system of arteries, toxins and work are among the important agents leading to medial lesions resulting in aneurysms.

From a clinical standpoint the presence of medial arterio-sclerosis is an indication to reduce as far as possible work and intoxications.

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THE NURSING PROFESSION.

I find the responsibility great; and the position, to discuss a subject of interest appertaining to you as nurses, a hard one to fill. While, I am on the Staff of this hospital my duties are such that we do not come in contact with each other. Our work is in different portions of the building,- mine where no history is taken. I have to do, not with the pitcher which has been cracked and still has hopes of going to the well, but when it is irrevocably shattered and its care has passed from your hands.

It has not been my privilege to have observed your progress while students at this hospital nor have I even now the opportunity of studying the outside conditions which each of you meets with, in pursuing your profession in the homes of strangers. I doubt not that the pleasures and sorrows, the successes and failures, which it is your lot to experience,

bear comparison with those of sister alumnae of other cities. On your graduation and departure from the well regulated hospital system,- an almost military training in discipline, you found things quite different in the outer world. You were now thrown upon your own responsibility and had to use your judgement between the doctors visits. There was no longer the opportunity to question or obtain a helping hand from Soror in Hospitals. You were obliged to do much in the Hospital, and most of all you had to enter into the spirit of the household, pleasing or otherwise as it might have been. This latter is the real test of character, and in a word, it frequently determines the career of the individual.

At the universities we have it repeatedly said that the gold medalist of the class seldom makes a success in his vocation. True or not as this may be, the inherent idea your comparisons with those of sister schools of other cities. On your graduation and departure from the well regulated hospital system,- an almost military training in discipline, you found things quite different in the outer world. You were now thrown upon your own responsibility and had to use your judgement between the doctors visits. There was no longer the opportunity to consult or obtain a helping hand from Doctor or Hospital. You were obliged to do much in the Hospital, and most of all you had to enter into the spirit of the household, pleasing or otherwise as it might have been. This latter is the real test of character, and in a word, it frequently determines the career of the individual.

At the universities we have it repeatedly said that the gold medalist of the class seldom makes a success in his profession. True or not as this may be, the inherent idea of the phrase presents much truth. In short a book knowledge of our work is inadequate in the practical competition of the world. But with you there is more still,- not only is it essential that you should know about those things (diseases) with which you come in contact; not only must you take charge and be able to carry out the physicians orders in the minutest detail, but you kust also present to the patient that kindly but firm character which commands respect.

It is hardly possible for anyone to discuss or even suggest the disposition and attitude of the nurse to the patient. Like the diseases you are treating,- no two characters are alike and each must be dealt with, according to his own peculiarities. Still less is it for me to discuss the loving tenderness exhibited in every female form, a virtue inherited as a 'maternal instinct,' that perfect of human feeling, shown most obviously it is true in the

tender and loving care of the mother for her offspring, but present in woman from the cradle to the grave; shown by the toddling infant towards its doll; in the motherly care of the older sister for the younger generation, shown in all possible relations of life in protecting the weak, nursing the sick and becoming the confidahr of the poor and needy, in teaching and leading upwards the young, in developing and supervising all orders of charitable and moral effort, and giving counsel and thought to the husband and everything that concerns his well being.

You who have chosen a profession whose first thought and aim it is to assist those in distress, to soothe the pain and ease the cares of helpless old age, command the greatest respect of all classes, rich and poor alike, and probably most of all, the men.

Life's cup is full of pleasures and tragedies, which present themselves in unequal proportion to mankind. Many are well fitted to

carry their burden without a murmur, and of these it is impossible to estimate their number or their cares. Others through misfortune, not entirely their own, cannot bear their load without assistance of those with more stalwart shoulders. It thus becomes the duty of each of us, who is more fortunate to be blessed with a healthy body, to give that helping hand to our less fortunate brethern.

I say it is our duty, not only from a point of honor but also in the general principles which preserve our being and our race. What each may do for another cannot be indicated by any mere rule or law. Laws are only for those who will not,-and rules guide those who know not how to do.

To us, however, whose duty it is to bring the sick back to a state of self control,- an independence by means of which these may again extend a helping hand to others,-to us, I say falls a heavy onus. In ministering to the sick we are assuming a responsibility to bring back into proper efficiency of life's task, those carry their burden without a murmur, and of these it is impossible to estimate their number or their cares. Others through misfortune, not entirely their own, cannot bear their load without assistance of those with more stalwart shoulders. It then becomes the duty of each of us, who is more fortunate to be blessed with a healthy body, to give that helping hand to our less fortunate brethern.

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If, for a moment, we cast a hasty glance over long periods of struggle through which the medical and nursing profession has progressed we must be particularly gratified at the progress which has been made during the last half century. Mankind has ever been suffering and has always needed those who will devote their energies in the uplift of those fallen by the way. It has been one of the conditions of life since the creation of man that there shall be suffering among men,- that there shall be sympathy granted by others. It has been this very fact that the needy are ever amongst us, which has developed in the hearts of man the sympathy towards all beings. True it is that the finer senses which have developed from the inborn kindly spirit, have altered much with the progress of time, and the development of new na-

tions. Sentiment is to be differentiated from kindness,- for much of sentiment is only the external manifestations of a riotous imagination.

We are apt today to see things only in a modern light, since we are brought up amidst certain surroundings and take much for granted. There is an order in all things about us which appears natural and which never calls to our mind the process of its formation. Mubh of that which appertains to medicine has come about in a process of evolution,-sometimes slowly, at other times with rapid strides. How we do admire the simple and sensible treatment of the fathers of medicine six hundred years before Christ. Their treatment was mainly of symptoms, but the remedies employed had the advantage that if unsuccessful, at least no injury was done. Prevention of disease was in higher favor then than it is now,- adequate bodily exercise, liberal use of baths, and attention to personal hygiene assisted much in developing a beautiful

race from whom the Venus de Medici was born.

Subsequent centruies cannot bost of this strict adherence to the use of the laws of nature. Much quackery was introduced into the practive of medicine in the middle ages. With it too the laws of hygiene fell into disuse until we had the unfortunate sequel to a squalid life,-the dissemination of infectious disease, the importation of epidemic diseases from Egypt and India, and the wholesale loss of life. This negligence of our ancient ancestors has cost the provinces of Eurpoe and unending source of distress. They have never again freed themselves of the plague, small pox or syphilis. It has thus involved the Western Countries in an enterprise to cope against disease which did not belong to them, and it has not only cost enormous sums of money but also a heavy toll of life before they obtained mastery over them. It is significant that the knowledge, concerning these plagued importations, has been gained through the

ceaseless efforts of the men of the west,-and not the wise men of the East.

One not infrequently obtains an altogether false impression from the figures of dry statistics, and I shrink from offering you any reports of my contention on vital statistics. It has however often impressed me that the ages of our forefathers much exceeded those of our people at the present time. You have no doubt had similar experiences, and felt justified in assuming that men and women of centuries ago lived a much longer span of life then we might hope for. This impression is still further strengthened by the unnumerable pictures of noted individuals made when they were in the winter of life, while seldom only was youth illustrated. Probably there are two reasons for this. Formerly man assumed adult vocations at a much earlier age than today, so that he grew old at forty. Not only was he advanced and mature at this age but he gave every indication of desolate effects of the war at the west,—not the least one of the many.

One not infrequently obtains an altogether false impression from the figures of [illegible] statistics, and I cannot refrain from offering you any reports of my own on vital statistics. It has however often impressed me that the ages of our forefathers much exceeded those of our people at the present time. You have no doubt had similar experiences, and felt justified in assuming that men and women of centuries ago lived a longer span of life than we might hope for. This impression is still further strengthened by the innumerable pictures of noted individuals made when they were in the winter of life, while seldom only were youths illustrated. Probably there are two reasons for this. Formerly men assumed adult vocations at a much earlier age than today, so that he was old at forty. [illegible] only had to [illegible] ture at this age but he gave every indication of the wear and tear of life making him a prematurely old man. On the other hand, too, lacking the knowledge of hygiene, treatment of disease and the care of the invalid, the majority of those falling ill, and more particularly the youth and those with weak constitutions, succumbed to the oft repeated plagues. The fittest survived,- but these were not necessarily strongest of the race when weighed in the intellectual balance. Necessarily there were many Homers, Ciceros, and Horace's perished in youth through negligence and lack of knowledge of disease.

In the wake of civilization, and in the increase in the population of every land there come the diseases which are difficult to combat. Close housing and squalid surroundings are certain to produce those unhygienic conditions in which disease is bred and propagated. The gradual spread of the Christian people from the southern provinces of Europe to the north had much to do with the reform of the native half-savage. Active attention to husbandry

changed the habit of the community from that of roving hunters to the settlement of districts. Farms were laid out, and domestic animals cared for,- while the more shrewd begun to barter with neighboring communities. Gradually, too, small villages and towns developed. Thus an active outdoor life was changed to a sedentary one. We have tried to force a similar change of life upon the Indian of North America. In each case there was a like result,- the visitation of plaques which threatened to exterminate the whole race. In medevial Europe the change in the mode of life was more gradual than with our Indian, who had unnatural conditions forced upon him. The former was therefore able to survive the pestilence,- the poor red man has been almost lost through tuberculosis, small pox and other infectious diseases. No laws of hygiene or of preventive medicine was theirs,- nor had those, who were afflicted, the opportunity of being nursed back to health changed the habit of the community from that of roving hunters to the settlement of districts. Farms were laid out, and domestic animals cared for,- while the more shrewd began to barter with neighboring communities. Gradually, too, small villages and towns developed. Thus an active outdoor life was changed to a sedentary one. I have tried to trace a similar change of life upon the Indian of North America. In each case there was a like result,- the visitation of plagues which threatened to exterminate the whole race. In medieval Europe the change in the mode of life was more gradual than with our Indian, who had unnatural conditions forced upon him. The former was therefore able to survive the pestilence,- the poor red man has been almost lost through tuberculosis, small pox and other infectious diseases. No laws of hygiene or of preventive medicine was theirs,- nor had those, who were afflicted, the opportunity of being nursed back to health.

by the care of those of your profession.

The literature gives us the accounts of several epidemics where this lack of medical aid and nursing skill was very apparent. In 1665 there swept through the continent of Europe an epidemic of plague. The cities were the main centers of the disease. From Italy to England human life was lost by the thousand, until the panic stricken people were desperate. These were in the prebacterial days. Nothing was known of the nature of the disease, and no means could be taken for its prevention. Ignorance fostered quackery. Many useless nostrums were advocated and the public were lead into supplying themselves with different highly odorous drugs to ward off contagion. Nursing of its kind was in vogue, but nurses were only called when the case was hoepless or to lay out the body when death occurred. As an extra fee was obtained for performing these last attentions it was not unwelcome to these unfeeling creatures.

The nurses were drawn from the ranks of widows and gossips of questionable reputation, and their's was a truly despicable life. In Kinsley's description of Old St. Paul in London a very good idea is gained of these hags who bartered in human life.

Similar conditions existed in many other cities of Europe while the plague existed. Almost the entire population of many towns was completely wiped out.

How do we stand today as regards the plague? We know the cause,- a bacillus; we can readily recognize the disease; we have a means of prevention. In the United States, as also in all civilized countries the ports are guarded by adequate hygienic inspectors to prevent the invasion of this disease.

Today what has the nurses to do with the hygienic success. We must answer 'very much.' Today every nurse is a first assistant to the medical profession. It is she who watches and sees

the course of disease at a time and times when the physician is unable to do so. Upon her observations must the doctor be guided in co-relating the symptoms, making his diagnosis and giving his treatment. It is by the nurses hand, that the little things, adding to the comfort and tranquillity of the patient, are carried out, and which are the life saving elements in many cases. Much depends upon the care of the nurse at the bedside whether a recent surgical wound will heal by first intention; upon her are the members of the family dependent whether the infection from an isolated case of diptheria will spread to others of the household. In a word, the carrying out of the details of our hygienic laws are in a great measure left in her hands. Proper care must be taken to disinfect all infectious excreta and thus prevent others falling prey to epidemic disease.

Again in another sphere of nursing the poor are directly attended. I refer to settlement work.

In this capacity the visiting nurse has the entire system of and the key to the hygienic situation under her finger. The ignorant and the poor need instruction in the fundamentals of sanitation; they need encouragement in their hard lot; particularly when one of the members of the family is severely ill. Moreover in many instances there is a display of an absolute lack of knowledge in household science and economies. For instructures in all of these essential domestic topics the visiting nurse is preeminently adapted. She has a welcome entre' to every household, and can insinuate helpful suggestions where instruction would fail. No form of municipal law could assist the needy as much as the practical exhibition of improved housekeeping by personal contact.

For those of you who have the personal incilnation for work of this order, I can only say, that you will be applying your lives to a

most commendable vocation. Many of our democratic institutions are still open to much reform, and we can take a valuable example in Mrs. Fry who lead the crusade against the unhygienic state of the prisons in England.

It was this very spirit of fraternal assistance which has lifted lay nursing from being a commercial profession to one of a higher order. The names of Fliedner, Fry, and Nightingale call to mind the revolution in the spirit of woman, to occupy a place in sphere of mankind compatable with her finer sense and commensurate with her energies. No one will deny the struggle which women have had, to obtain recognition for that which they are in every nature fitted. Her field essentially amidst the duties surrounding our happiness and well being. Whether she would aspire to sail on the rough sea of commerce and finance, is open to much discussion.

However, possibly it is not proper, being associated and conversant with some of great

work, that I should presume to give a personal opinion upon its merits. Our every day surroundings are apt to make us short sighted,-we see the good,- we overlook the shortcomings.

To you national boundaries have no meaning, social customs present no bars and creed form no obstruction. You are led into your life's work by the needs of the community, and not by any political demand or preferential trade. With you love for your work and the enthusiasm to do good, you will be happy and quite oblivious of strife in the manacled world of commerce.

If amidst your arduous and care-wearing duties you are able to retain that broadening spirit, which allows you to see the good of others your position becomes ideal. Happy in your work, contented when at leisure. Everyone appreciates the depressing effect of continuous contact with a pessimistic or worse still a melancholic patient. His sullen spirit seems contagious until to us the cloud has lost its silver lining. It

requires a particular effort on our part to keep our spirits boyant, lest we lose the confidence not only of the patient but also of ourselves.

On the other hand, who of you has not had much quiet amusement at the oddities of your patient, or have even indulged in hearty outbursts of laughter at the convalescents expense? Who has not blushed at the frank and outspoken family secrets divulged during the anaesthetic? Some no doubt have even promised themselves to keep notes of the witticisms and pleasantries heard at the bedside. These, however, would be only for your eyes, for everything seen or heard while on professional duty is sacred. Much as we would like to have another enjoy these cases of amusement with us, they are forbidden words. Sometimes however the patient turns the tables on us and finds much to interest, as well as to amuse, of which he writes others.

A few years ago there was lost to us a writer whose word should have some interest

to the profession. He, through a long protracted illness in a hospital, came in close contact with much relating to medicine, and although his word has a pessimistic ring there is much truth in his verse,- truth as seen from the patients attitude. Henley was a poor individual, not endowed with riches which would allow him the luxuries of the private ward.

His little book of verses,"In Hospital" are not widely distributed, but his apt delineation and keen observation of hospital dicipline make it particularly appealing to us. Henley was a patient in Listers wards in the Royal Infirmary at Edinburgh in 1874. He had recently graduated from St. Andrews, and made an unsuccessful attempt at journalism and as a writer of verses. Now at the age of twenty-five he was to become a hopeless invalid. Much that he saw in the hospital was evitently new and made a deep impression. He describes the admission of patients

A small, strange child - so aged yet so young!
Her little arm besplintered and beslung,
Precedes me gravely to the waiting room,
I limp behind, my confidence all gone,
The gray-haired soldier waves me on,
And on I crawl, and still my spirits fail;

While waiting to be admitted in turn, he sits upon

"... a bench a skeleton would writhe from,
Angry and sore, I wait to be admitted;
Till my heart is lead upon my stomach,
While at their ease two dressers do their chores.

Then he is admitted to the surgical ward where, there is nothing of home."

The atmosphere
Suggests the trail of a ghostly druggist,
Dressings and lint on the long, lean table-

After due consideration it was determined that his limb required operation; and he spends some time before the event in analysing his feelings.

"Behold me waiting - waiting for the knife,
A little while, and at a leap I storm
The thick, sweet mystery of chloroform,
The drunken dark, the little death-in-life."

Then he is taken to operating room:-

"You are carried in a basket,
Like a carcase from the shambles,
To the theater, a cockpit
Where they stretch you on a table."

"They bid you close your eyelids,
And they mask you with a napkin,
And the anaesthetic reaches
Hot and subtle through your being.'

After the operation is over he comes out of the anaesthetic:-

Like as a flamelet blanketed in smoke,
So flashes and so fades my thought, I heave
and choke
And sicken at, it is so foully sweet.
Then my senses fleet:
All were a blank, save for this dull new
Pain
That grinds my leg and foot.

Then ther is a long convalescence during which:-

"Shoulders and loins
Ache.............!
Ache, and the mattress,
Run into boulders and hummocks,
While the bedclothes....ramble and roll."
At night
Far in the stillness a cat
Languishes loudly. The next man to me
Turns with a moan; and the snorer,
The drug like a rope at his throat,
Gasps, gurgles, snorts himself free,
as the night-nurse,
Noiseless and strange,
Whispering me 'Are you no sleeping yet?'
Passes:-

Later in his leisure hours he describes those about him:-

Of the Staff nurse he says:-

"The great masters of the commonplace,
REMBRANT and good SIR WALTER - only these
Could paint her all to you: experienced ease
And antique loveliness and ponderous grace;
These thirty years has she been nursing here,
Some of them under SYME, her hero still.
Much is she worth, and even more is made of her.
Patients and students hold her dear,
The doctors love her, tease her, use her skill
They say, "The Chief" is half afraid of her."

To him the probationer has quite a different air:-

"A Roman nose; a dimpling double-chin;
Dark eyes and shy that, ignorant of sin,
Are yet acquainted, it would seem with tears
A comely shape; a slim, high-colored hand,
Graced rather oddly, with a signet ring;
A bashful air, becoming everything;
A well-bred silence always at command.
Her plain print gown, prim cap, and bright steel chain
Look out of place on her."

And thus he goes on to discuss what is the common place with us. He like every patient observed and was impressed by the changes which have been wrought in medicine, in the care and treatment of patients. Probably our own conception of our work, and of those in the same profession, would be more acute if in the case of illness we were to take their places.

And now I close this somewhat rambling discourse, and repeat again the high esteem in which your work is held. The success of each lies in her own doing, - and work, more than enough is waiting those willing to take hold. At no time must we shirk those duties for which our profession has trained us.

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INFECTION BY THE GAS BACILLUS IN COAL-MINES

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INFECTION BY THE GAS BACILLUS IN COAL-MINES.*

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The discovery by Professor Welch in 1891 of *B. welchii*, and the observed relationship of this organism to the production of gas in the tissues was the first definite evidence that the inflation of tissues before and after death was commonly due to bacterial invasion. The presence of free gas in various parts of the body has been commented upon in the literature by many of the older writers, and for some time it strengthened the belief that air was an important constituent of the circulation. Simple putrefaction was suggested by others as the cause of the accumulation of this gas. On the other hand, prior to Welch's discovery, we have the observations of Pasteur, Koch, and their pupils, which indicate that a type of organism was found and known to them which in all probability belonged to the *B. welchii* group.

Welch and Nuttall published their first report in 1892. Then there followed a series of observations from the laboratories at Johns Hopkins Hospital indicating the wide distribution of this organism in nature and disease. Almost simultaneously there appeared in Germany and France similar observations by Fraenkel, Ernst, Goebel, Dobbin, and others. The importance of this type of infection was emphasized by each, and the danger of its presence in deep wounds, particularly when associated with other pyogenic bacteria, was appreciated by the surgeon. With, however, the improved technic in bacteriology, along with keen interest for the isolation of new anaerobic forms, we find that several investigators determined the presence of organisms, simulating in many respects *B. welchii*, but on account of finding them in new locations and of slight, possibly transient variations, applied a new nomenclature. Thus Fraenkel, finding a large anaerobic bacillus in gaseous phlegmons gave it the name *B. phlegmones emphysematosae;* Veillon and Zuber isolated bacilli from cases of otitis media, pulmonary gangrene, mastoiditis, appendicitis, and pelvic abscess which they

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called *B. perfringens;* Lindenthal, in 1897, isolated an organism from the emphysematous tissues about the vagina, to which he gave the name *B. emphysematis vaginae.* Likewise to an organism isolated from milk and water and having characters of *B. welchii,* Schattenfroh and Grassberger gave the name *Granulobacillus saccharobutyricus immobilis liquefaciens.*

No general systematic study has been undertaken to determine which of these organisms are identical with or belong to the group of organisms of which *B. welchii* is the important representative. It is probable that the slight variations which have been observed in these somewhat similar organisms are real, but it is plain that, with the meager information obtainable for many of them, no very definite statement can be made for their isolated identity. To this uncertain class might be added *B. vaginae* (Kruse), *B. cadaveris* (Sternberg), and *B. cadaveris butyricus* (Buday). It is also evident that many of the cases of human infection which have been described in America as malignant edema are instances of infection by the *B. welchii.* Clinically, some cases presenting features of malignant edema with progressive gangrene, in which very little gas can be demonstrated in the tissues, show on bacteriological examination the presence of the "gas bacillus" along with other organisms.

Some confusion has also arisen between *B. welchii* and *B. enteriditis sporogenes* (Klein). The latter organism has been isolated by Klein from a great number of sources (sewage, manure, feces, street dust, milk, etc.). This organism has certain characters which distinguish it from the organism of Welch, particularly to be observed in the presence of flagella and motility. Klein reports the ease with which spores are produced in tissues; but this appears to vary with certain strains, and in cultures is equally difficult to obtain as with *B. welchii.* Again it is pointed out that *B. enteriditis sporogenes* is highly virulent, but this too is not constant, as the cultures of the organism may rapidly lose their virulence. There is, however, a striking resemblance between the organisms of Klein and that of Welch in the production of gas in the animal tissues. By using the same procedure as Welch of inoculating the organism into the veins and then killing the animal and incubating, Klein has found that *B. enteriditis sporogenes* produces much gaseous emphysema throughout the body. Another feature in which these organisms resemble each other is the sparse growth of thin translucent colonies on surface agar.

A most comprehensive study of the "Morbid Conditions Caused by *Bacillus aerogenes capsulatus*" is given by Professor Welch in his Shattuck Lecture of 1900. It is pointed out by Welch that the duplication of nomenclature has led to much confusion in the discussion of the bacteriology of emphysematous gangrene. This we have met with in our study, but it has also appeared to us that *B. welchii* constitutes a group of organisms, each of which may produce gas in tissues, and have some slight variation in morphological or cultural features.

Our attention was attracted to this infection by the unusual frequency of emphysematous gangrene occurring in the surgical wards of the hospitals in Pittsburgh. For the clinical data we are indebted to Drs. R. W. Stewart, J. J. Buchanan, G. L. Hays, A. Stewart, and J. P. Griffith, surgeons at the Mercy Hospital.

The reports of the cases comprising this study have been taken from the records of the Mercy Hospital at Pittsburgh. There are 36 cases in all, in which both the clinical and bacteriological examinations demonstrated the presence of *B. welchii* or one of the members of this group. A number of other cases in which a satisfactory analysis of the bacterial infection was not forthcoming were not included, although we felt that some of them at least were infections by the gas bacillus. These latter cases gave clinical evidence of gas in the tissues at the point of injury, some also showing indurative edema with gangrene, but a bacteriological examination had been omitted. These cases must remain in the undetermined class, but we feel with Welch that the production of gaseous gangrene in life is in the majority of cases due to the infection of *B. welchii* or one of the members of this group, and that gas formation in tissues by *B. coli* remains unproved, save possibly in a few reported cases of diabetes. Concerning infections by the bacillus of malignant edema in man, we have had no experience, and believe that authentic cases of this condition in America are extremely rare.

As the hospital from which our records are taken does not admit maternity cases we have no instance in this series of uterine infections by *B. welchii*.

TABLE I.

Number	Age	Sex	Occupation	Nature of Accident	Nature of Wound	Result
1......	27	Male	Bridge-builder	Fall from bridge	Comp'd fracture of arm	Recovery
2......	31	Male	Telephone lineman	Fall from pole	Comp'd fracture of arm	Recovery
3......	20	Male	Coal-miner	Run over by car in mine	Comp'd fracture of ankle	Recovery
4......	14	Male	Coal-miner	Run over by car in mine	Comp'd fracture of both thighs	Recovery
5......	28	Male	Coal-miner	Fall of slate in mine	Comp'd fracture of fibula and tibia	Death
6......	24	Male	Laborer	Accident at steel works	Comp'd fracture of leg	Recovery
7......	42	Male	Coal-miner	Fall of slate in mine	Crush of foot (open wound)	Death
8......	16	Male	Mill worker	Accident at steel works	Crush of foot (open wound)	Recovery
9......	72	Male	Coal-miner	Crush by cars in mine	Laceration of leg (open)	Death
10......	31	Male	Coal-miner	Crush in mine	Comp'd fracture of leg	Death
11......	19	Male	Brakeman	Crush by train	Comp'd fracture of hand	Death
12......	54	Male	Coal-miner	Crush in mine	Comp'd fracture of leg	Death
13......	29	Male	Coal-miner	Crush by cars in mine	Comp'd fracture of leg	Recovery
14......	25	Male	Coal-miner	Crush by car in mine	Comp'd fracture of femur	Death
15......	25	Male	Electrician	Fall from scaffold at a mill	Comp'd fracture of radius	Recovery
16......	23	Male	Coal-miner	Fall of slate in mine	Comp'd fracture of fibula	Recovery
17......	45	Male	Coal-miner	Fall of slate in mine	Laceration of foot	Recovery
18......	31	Male	Coal-miner	Crush by car in mine	Left thigh almost severed	Recovery
19......	21	Female	Housewife	Fall from porch	Cut forearm in glass on ground	Recovery
20......	19	Male	Laborer	Explosion of powder	Fracture of leg with laceration	Recovery
21......	23	Male	Mine driver	Crush by car in mine	Comp'd fracture of both legs	Recovery
22......	36	Male	Mill worker	Crush in mill	Comp'd fracture of both legs	Recovery
23......	17	Male	Coal-miner	Crush by car in mine	Comp'd fracture of leg	Death
24......	28	Male	Laborer	Fall into ditch 15 ft.	Comp'd fracture of femur	Death
25......	9	Male	School boy	Fall from ladder	Comp'd fracture of forearm	Recovery
26......	23	Male	Machinist	Fall from box-car	Comp'd fracture of humerus	Death
27......	39	Male	Coal-miner	Injured by mine truck	Comp'd fracture of tibia	Recovery
28......	32	Male	Coal-miner	Crush in mine	Thigh lacerated	Death
29......	9	Male	School boy	Fall from tree	Comp'd fracture of forearm	Death
30......	40	Male	Laborer	Train accident	Crush of left arm	Recovery
31......	38	Male	Coal-miner	Fall of slate in mine	Comp'd fracture of ankle	Recovery
32......	30	Male	Laborer	Run over by street car	Crush of left leg	Death
33......	15	Male	School boy	Run over by train	Crush of legs	Recovery
34......	61	Male	Coal-miner	Crush by car in mine	Laceration of thigh	Death
35......	24	Male	Coal-miner	Crush by car in mine	Crush of heel	Recovery
36......	24	Male	Coal-miner	Fall under car in mine	Comp'd fracture of both legs	Death

Gas present in tissues in all cases.

In summarizing the above 36 cases we find that there were 35 males and one female. The youngest individual was nine years and the oldest 72 years. The average age was 31 years. Every case in the series had a severe external wound. There were 23 cases with compound fractures. Of these, 16 were of the lower and seven of the upper extremity. The remaining 13 cases consisted of severe lacerated flesh wounds in which no bones were broken but in which extensive areas were laid bare to infection of all kinds. The very nature of these accidents where great mechanical injury was received, led, in nearly all cases, to the fall of the individual to the ground. It is this feature, the pollution of the wound by the infected soil, in many instances the dirt being ground into the tissues, which makes these lesions very susceptible to this form of infection.

More interesting, however, is the evidence of occupation susceptibility. Of the 36 cases which we here report, there were 20 coal-miners who received their wounds while at work in the mines. The accidents leading to the extensive lacerations were of two kinds: (1) the falling of the slate from the roof of the mine upon the workman; or (2) crush-accidents between or under the mine cars. In either case the individual received lacerations with large open wounds which readily became infected by the soil of the mine. Temporary first-aid treatment was received in the mine. The severe wounds were later given hospital treatment. Gas in the tissues about the wound was observed to occur as early as 12 hours, and as late as four days, after the accident. Of the entire 36 cases reported, 40 per cent proved fatal, while of those receiving their injury in the coal mines, the mortality was 50 per cent.

Of the remaining 16 cases not working in the mines there were:

Laborers	5	Electrician	1
School boys	3	Brakeman	1
Mill workers	3	Telephone lineman	1
Bridge-builder	1	Housewife	1

In all instances but one, the injuries were received while the individual was out-of-doors, and in the majority of these 16 cases the wounds were obtained on the street or some driveway or in a garden. Two of the school boys were injured in a fall in a garden, from a ladder and a tree respectively. The injury, with gas-bacillus infection in a woman, was received in a fall from a porch on to the garden soil. Three individuals were injured in railroad accidents, in which the lacerated wounds were soiled by the earth along the railroad tracks. One case developed tetanus after the appearance of gaseous emphysema.

It is significant in all of these cases that the wounds were infected by earth, dirt, or materials which themselves were open to fecal pollution from either man or animals. It is obvious that the highways are repeatedly reinfected by various pathogenic organisms, and although sunlight and rain greatly assist in removing from the surface the presence of living bacteria, a great variation exists in the extent of this disinfection. The presence of moisture, shade, and porous organic substances assists greatly in preventing the destruction of many bacteria. Great variation, too, exists among the individual organisms in their resistance to external destructive influences, so that soil and dust, although subject to climatic changes, commonly contain an abundance of spore-bearing bacteria and such other organisms which are not so readily affected by variable temperature and light.

It has been demonstrated by many observers that *B. welchii* and its closely related forms are almost constant inhabitants of the intestines of both man and animals. Welch and Flexner, Clopton and Howard have isolated this bacillus from the intestines of man, while Welch has also demonstrated its presence in the bowel of rabbits, dogs, and swine, and Houston obtained it in cow dung. Walker isolated the organism from the dust of hospital wards; Harris has found it in the contents of cesspools, and Fraenkel has obtained it in a splinter of wood which had led to an emphysematous infection of a wound. We have isolated a gas bacillus with characters of *B. welchii* from rich garden earth, and we have also obtained it from the tissues of a cadaver undergoing putrefaction in whom no external wound of entry existed. It is evident, therefore, that this bacillus is widely disseminated in nature and that the contamination of the soil will continue to exist in such localities where repeated fecal pollution takes place.

In being confronted by the evidence of the high incidence of infection by the gas bacillus in coal-mines, it was obvious that the bacterial contamination had been carried into the mine subsequent to its opening and development. The conditions that are present in the majority of these mines are favorable for the development and protection of bacteria which may find their way into the mine. The protection from light, drying, and excessive ranges of temperature permits the bacteria to persist for long periods of time in the damp soil.

In the examination of a coal-mine in which mules were used in the most distant underground workings, we had no difficulty in isolating *B. welchii* from the soft earth in several of the paths along which they traveled. It is probable that even when these animals are taken from a certain route the ground infection from the feces persists for a considerable period. Moreover, a certain amount of distant dissemination of the organisms takes place through the trickling of water and the carriage of the organism on the shoes of the laborers along many of the paths. It was found, too, that the men polluted the abandoned rooms or a portion of a room from which coal was being taken, by defecating in them. This practice leads to the distribution of large numbers of bacteria of all kinds to a region where there is a natural absence of organisms. Moreover, the injuries received by the miners by falling slate or coal were in the majority of instances received in the working rooms where this human pollution is found; while on the other hand, the injuries obtained about the truck cars were in the galleries where the mules are, or formerly were, frequently passing to and fro.

It seems quite obvious, therefore, that infection by *B. welchii* and other bacteria in coal-mines is a direct outcome of fecal pollution of the ground by man and animals.

It has been repeatedly noted at autopsy that much hemolysis occurred in individuals infected by the gas bacillus. The blood within the vessels is laked, and the vessels immediately after death, and probably during life, show a cherry-red staining of the tissues. Not only do the blood vessels show this hemoglobin imbibition, but it is also to be observed in the parenchymatous organs. Our observations on the hemolytic effect of our cultures on blood agar is in agreement with these vital findings.

More definite evidence of the effect of the gas bacillus upon the red blood cells is brought forward by the clinical blood examinations carried out under the direction of Dr. G. L. Hays. We are much indebted to Dr. Hays for the privilege of using some of his records of blood counts. It is quite obvious that, on account of the nature of this infection, there is quite a variation in the constitutional reaction in different individuals.

In some cases the infection is very localized, in others the emphysematous gangrene spreads progressively, while in the very severe cases the organisms soon become invaders of the blood stream. In like manner, the effect upon the blood-cells is directly dependent upon the absorption of the hemolysins from the infected site, the blood infection naturally being the most severe.

November 1, 1910......	Coal miner, adult, 39 years. Compound fracture of tibia by a coal car in the mine. Arrived at hospital seven and one-half hours after injury was received.		
November 3, 1910......	*B. welchii* was isolated		
	Red cells	3,450,000	Hemoglobin
	Leukocytes	17,800	
November 6, 1910......	Red cells	3,240,000	Hemoglobin 78 per cent
	Leukocytes	19,420	
November 7, 1910......	Red cells	3,190,000	Hemoglobin 78 per cent
	Leukocytes	20,400	
November 8, 1910......	Red cells	2,880,000	Hemoglobin 76 per cent
	Leukocytes	20,000	
November 9, 1910......	Red cells	2,170,000	Hemoglobin 73 per cent
	Leukocytes	15,120	
November 13, 1910......	Red cells	2,220,000	Hemoglobin 75 per cent
	Leukocytes	13,250	
November 15, 1910......	Red cells	2,280,000	Hemoglobin 75 per cent
	Leukocytes	11,200	
November 17, 1910......	Red cells	2,940,000	Hemoglobin 77 per cent
	Leukocytes	10,920	
November 19, 1910......	Red cells	3,130,000	Hemoglobin 77 per cent
	Leukocytes	9,800	
November 22, 1910......	Red cells	3,440,000	Hemoglobin 78 per cent
	Leukocytes	9,400	
November 26, 1910......	Red cells	3,840,000	Hemoglobin 81 per cent
	Leukocytes	8,000	
December 11, 1910......	Red cells	4,680,000	Hemoglobin 84 per cent
	Leukocytes	7,800	

Recovery

In two other cases blood counts were similarly carried out. In the one, the red cells fell to 2,590,000, in the other to 4,000,000. It was observed in each case that the greatest anemia was not immediately after the accident when a certain amount of hemorrhage occurred, but the fall in the red cells was progressive from day to day until the infection was overcome and convalescence was taking place. It is quite probable that this secondary anemia is an important factor in determining the issue of this infection. It is apparent, too, that much of the hemoglobin continues to circulate with the blood, the liver and the spleen being unable to remove the quantity liberated.

BACTERIOLOGICAL.

The isolation and determination of *B. welchii* from infected wounds is attended by considerable difficulties. The first and majority of the cases here reported were determined by the simple methods described by various authors, and which can be only taken to indicate the presence of one of the members of the gas-bacillus group. In the last nine cases attempts were made to isolate the organisms in pure culture and to determine the cultural characteristics of each. It has been our experience that these infected wounds always harbored mixed cultures. In one instance a pure culture of *B. welchii* was obtained from the heart blood at autopsy. The wound (compound fracture of the leg) contained several types of bacteria, including *B. welchii*, but the gas bacillus was the only one which invaded the blood. As this autopsy was performed one hour after death it is probable that the organism began its invasion of the systemic circulation during life. Streptococci are probably most frequently associated with the infection by the gas bacillus, and it is even suggested by some that *B. welchii* requires this or some other organism to produce conditions favorable for its growth in the tissues. Welch, however, has shown that aseptic lesions, presenting areas of less resistance, readily become the nidus for the gas bacillus, and that, therefore, a primary infection of a different nature was not essential. The nature of the bacteria present in a lacerated wound is obviously dependent upon the bacteria present in the contaminating materials. Hence, the types of the organisms which may be associated with *B. welchii* are very numerous.

In the usual routine the determination of the infection in a case of gaseous emphysema has depended upon both a clinical and preliminary bacteriological examination. The presence of a lacerated wound, not in the region of the lungs or air passages, showing a progressive infiltration with gas, along with more or less edema and gangrene, from which the smears show large gram-positive bacilli with rounded ends and occasionally showing spores and capsules has, along with the cultural production of a "stormy fermentation" in milk, been indicative of a gas bacillus infection. To this, the presumptive test of gas production in the tissues of an animal which had been inoculated, killed, and incubated, has been of further confirmatory value.

It is evident from the reports of Klein that other organisms belonging to this group may produce gas in the tissues, so that the presumptive test by the inoculation of material into the tissues of an animal with subsequent gas production does not prove the identity of the organism but rather of a group of organisms.

It has been observed by others that some confusion has arisen on account of the varying staining reactions exhibited by this organism. We have noted that *B. welchii* stains readily with the simple stains, and that the majority of the organisms obtained from the infected tissues are gram positive. In such smears a few bacilli lose the gram stain. The organisms, however, taken from older cultures have a most irregular action to this stain. In some cases the majority may be gram negative while others contain gram-positive masses or show a polar staining. The older cultures tend to become gram negative, but fresh cultures from these may again give rise to gram-positive organisms. It was observed, however, that certain cultures had a greater tendency to produce irregular staining and gram-negative forms than others. In a like manner there is some difficulty in obtaining uniform results with the capsule stain. We have found that capsules are best demonstrated from the fresh tissue and from the growths on Loeffler's blood serum.

B. welchii is non-motile. Spores are not readily formed. We have observed them both in fresh smears from the tissues and also in cultures on Loeffler's blood serum, but they are seldom present in abundance. In one strain isolated we have obtained spores in cultures with comparative ease.

In our later cases we have isolated *B. welchii* in pure culture and determined the cultural characters. These have corresponded to the characters described by Welch, and to them we have added a number of other features which may be of assistance.

For the production of anaerobism we have used the pyrogallic-acid method, while for the separation of mixed cultures we have used the deep-agar (dextrose) shake method. In almost all cases it was necessary to repeat the process for separation several times before an individual pure colony could be picked. This was then planted in media for the differentiation. It was observed that the complete fermentation of the various media occurred very rapidly and that no further change took place in the media after 48 hours. The inoculated gelatin was incubated with the other tubes, and after removal from the incubator it was chilled in the refrigerator. By this means growth was always obtained and the complete liquefaction of the gelatin occurred in 24 to 36 hours; when, however, the gelatin cultures were permitted to develop at lower temperatures, the growth and liquefaction were very much slower. We believe that if the method of incubation is used for gelatin cultures, uniform results of liquefaction of this medium will be obtained for this organism. The following characters and reactions on media were obtained when *B. welchii* was grown anaerobically:

Broth	Poor growth at bottom of tube. Upper liquid clear
Agar slant	Fine discrete translucent gray colonies of less than pin-head size
Blood agar	Fine discrete gray colonies with hemolysis
Gelatin	Complete liquefaction
Dunhams	No indol. Growth poor
Dextrose broth	Acid and gas
Lactose broth	Acid and gas
Saccharose broth	Acid and gas
Mannite broth	No acid and no gas
Potato	Invisible—sometimes a moist appearance along line of inoculation
Milk	Acid and coagulation with gas. "Stormy fermentation." Strong odor of butyric acid
Loeffler's blood serum	Moist gray colonies, sunken below the surface. Liquefaction of the medium continues

The fermentation of various sugars can also be observed in stab or shake agar to which the various sugars have been added. In such agar tubes the fermentation was at times so great as to force the plug and some of the agar out of the tube. The surface colonies were found to rapidly lose their vitality so that further transfers from them were unsuccessful. The inoculation of the organism into the blood stream of the small animals gave rise, after death, to a great production of gas in the tissues of the entire body. From these tissues the bacillus was again isolated.

In an attempt to do away with animals in these experiments, we introduced the bacillus into fresh liver tissue obtained from the butcher. Both beef and calf livers were used, and although a production of gas was obtained in them, we found an equal amount produced in the uninoculated controls. From these control portions of the liver, a gram-positive bacillus was obtained closely resembling *B. welchii*, but we have not up to the present been able to isolate it in pure culture. These microorganisms with the production of gas in beef and calf livers were obtained in six different controls and precluded the use of these tissues for these experiments. We similarly encountered difficulties in the use of guinea-pig liver. In the latter instance, some of the liver of a guinea-pig was removed sterilely and placed in the Smith fermentation tubes to facilitate the anaerobic condition. We found, however, that this too was impractical, in that there was a gas production in the uninoculated liver, with the growth of a gas-bacillus-like organism. These results are very similar to those of Wolbach and Saiki who found that the healthy livers of dogs contained bacilli growing only anaerobically.

From one of the human cases there was isolated an organism with the general characters of *B. welchii* and which by the simple methods would have been classed as this bacillus. It was found, however, to be quite distinct in its cultural characters from the one above described.

The organism was obtained from the lacerated wound of a compound fracture which ended fatally, and by means of anaerobic shake cultures it was separated in pure culture from streptococci and from gram-negative aerobes. The bacilli were large organisms with blunt ends and rounded corners. They stained readily with ordinary stains and were gram positive. Spores were observed in the original material and were also seen later in old serum cultures. The organism usually appeared singly or in pairs, seldom in chains. Cultures were only obtained by anaerobic methods. Motility was observed in fresh cultures. The cultural characters were as follows:

Broth	Very scanty growth at bottom
Agar	Thin transparent grayish growth along streak
Gelatin	No liquefaction
Potato	Much gas in fluid below medium; surface of medium moist; colony invisible
Dunhams	No indol
Litmus milk	Acid with firm clotting, gas and clear whey, odor of butyric acid. No softening of clot
Dextrose broth	Acid and gas
Lactose broth	Acid and gas
Saccharose broth	Acid and gas
Mannite broth	No acid, no gas
Dulcite	No acid, no gas
Loeffler's blood serum	Fine gray colonies with gray flocculi in the water condensation. No evidence of liquefaction

Animal test.—The inoculation of the organisms into the circulation led to a great distension of the tissue and organs with gas (18 hours after the death of the animal).

Subcutaneous inoculation of the organism into the healthy tissues of a rat was without effect.

We have, then, to deal with an organism belonging to the gas-bacillus group, but differing from the bacillus of Welch in the presence of motility, the non-liquefaction of gelatin and blood serum, and the readiness with which it produced spores on serum media. Spores were also observed in the colonies of deep-agar shake cultures. The surface colonies on agar were more diffuse and not so discrete as those of the true *B. welchii*. It simulated closely *B. butyricus* of Botkin as described by Klein.

SUMMARY.

There appears, from our findings, to be an unusual frequency of infection by the gas bacillus among those receiving lacerated injuries in the coal-mines. This infection gives all the clinical manifestations of gaseous phlegmon while the bacteriological analysis indicates the presence of a member of the *B. welchii* group of organisms. These organisms, save one, which we have been able to isolate in pure culture and cultivate on differential media, conform with the characters of the *B. welchii* which have been described by Welch. One strain of organism was isolated which had many of the characters of *B. butyricus* of Botkin.

In the light of Klein's work on *B. enteriditis sporogenes* and *B. butyricus* of Botkin and with our isolation of an organism belonging to the gas-bacillus group having, however, definite characters separating it from *B. welchii*, it is evident that other anaerobic bacteria, simulating in many respects the gas bacillus of Welch, may produce an emphysematous gangrene in man. In all probability, therefore, the infection by the so-called gas bacillus indicates a disease produced by a group of organisms with many features in common rather than by a single organism.

The clinical observations of the rapid destruction of the red blood cells during life in these infections is of great interest, and is probably associated with the rapidly fatal course in many cases. The hemolytic effect may also be observed in cultures.

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DISCUSSION ON SYMPOSIUM ON LARYNGEAL NEOPLASMS.

(State of Penn. Med. Soc. 1910.).

By

Oskar Klotz.

I voice the concensus of opinion in saying that we have been much pleased by the papers and the practical discussions in them. Many, no doubt, have been impressed in the discussions with the difficulties which arise in making a diagnosis of a neoplasm appearing in the respiratory tract. This difficulty besets not only the clinician but also the pathologist. But the advances which have been made on the clinical side for observing and determining the nature of the lesions occurring in the larynx and the air passages have, in late years, been much more rapid than those that have been made by the pathologist for diagnosing these conditions. With the advent of the bronchoscope and other instruments, the clinician is armed that he can carefully ob-

serve all changes occurring in the larynx and trachea below, With this information that he thus gains, he is often in a better position to make a diagnosis than is the pathologist, who sees not the organ affected, but a most minute portion of the diseased tissue.

It appears to me that Dr. Grayson has struck a true note in his discussion on difficult diagnoses. It too frequently happens that the pathologist is asked to make a conclusive diagnosis from small snippings taken from the larynx. Such a procedure is almost hopeless and we must agree with Dr. Grayson that prior to submitting any material to the pathologist, the clinician must gain all the evidence available that may assist in coming to a proper conclusion as to the nature of the case. Moreover, the final summing up of all evidence available both from all the clinical sources and from the laboratories be made by the clinician.

There is possibly one suggestion that we may offer in the way of an explanation - not an apology - for the at-times unsatisfactory pathological reports. This suggestion is that a sufficient amount of material be sent to the pathologist for study. From experience, we have learned that, for the proper study of tissues, we must have such an amount of material as will show the relationship of the various structures. We have learned that under normal conditions, the cells of every tissue occupy a certain relative arrangement to their neighbors and more particularly is this true of the arrangement of the epithelial cells to their underlying connective tissue. The study of the epithelial cells can not be undertaken by observing the epithelial cells alone, but must be made of the various layers of epithelial cells, particularly the deepest layer where this tissue comes in contact with cells of a different nature, It is this deepest epithelial layer which indicates changes due to external influences, and it is

moreover this malpighian layer which shows the early changes of malignancy under the microscope. In obtaining snippings, therefore, from any epithelial surface, it becomes essential to have a portion of this deep tissue included, to estimate the conditions and changes which exist among the epithelial cells and their relation to the submucosa. It is from tissue masses, taken superficially, which do not include the submucosa that reports unsatisfactory to the clinician are obtained from the pathologist. It is true that even with these favorable circumstances, in which the tissue has been properly obtained, the pathologist meets with some difficulty in distinguishing certain inflammatory reactions from malignant growth. Dr. Kyle appeared rather skeptical as to the possibility of distinguishing new growth from specific lesions in the laryns. But I would here repeat what I have said above that, if the clinician brings together all the available facts con-

cerning the case and uses the newer clinical methods for distinguishing various types of granuloma, much information will be gained before the pathologist is approached, and much information can be given the pathologist which will aid him in coming to a proper conclusion.

As Dr. Boyce has pointed out, there are some instances in which distinction between granulomatous masses and true new growth is made, both clinically and histologically, with great difficulty. However, at the present day, we have at our command tests, which to a certain degree indicate one or other of the specific infections. The Wassermann reaction is quite sencitive in distinguishing the presence of syphilitic lesions in the body, and likewise the tests are very sensitive for tuberculosis. However, in applying these tests, they only indicate the presence of specific infection in some parts of the body and do not necessarily point to a given organ, but in obtaining evidence from these tests, we are adding one more point for the

final summing up of the case. In the few syphilitic laryngeal lesions, which I have had the opportunity of testing, all gave a positive Wassermann reaction.

From the pathological standpoint, the important tumors or neoplasms in the larynx are of an epithelial origin or arise from the tissue immediately beneath the epithelium.

Broadly, they may be classified into the benign and malignant. Of the former the fibroma and papilloma are the commonest. In discussing the papilimata, there are, as Dr. Jackson has indicated, two types, one arising in the early yeats of life and the second arising after adolescence and usually having an inflammatory lesion preceding it. The papillomata arising in the early years of life have an apparently tendency in that they recur when removed. As far as is known, these tumors have not malignant qualities of metastasis when first observed, but it is claimed that the growth may at any time thial covering $\frac{1}{5}$ of the case. In the few syphilitic laryngeal lesions, which I have had the opportunity of testing, all gave a positive Wassermann reaction.

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This type of neoplasm, the recurrent papilloma, presents the greatest difficulty for making a diagnosis and determining the presence of malignant qualities. Just as the clinician character of the tumor varies between a rapidly growing benign and a form of malignant growth, so too the histological characters persent all transitions of these two types of neoplasms.

In a case of striaght-forward epithelioma of the larynx, no histological difficulty is encountered, but here, too, care must be taken to obtain tissue masses extending to some depth beneath the surface. Preferably all snippings should be taken as nearly as possible at right assume malignant qualities. Sir Felix Semon has cultivated a number of such recurrent papillomata taking on the destructive invasion tendency as is seen with epitheliomata. If such be truly the case, then we have another evidence that certain benign growths may gradually develop into neoplasms of a malignant nature.

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In a case of straight-forward epithelioma of the larynx, no histological difficulty is encountered, but here, too, care must be taken to obtain tissue masses extending to some depth beneath the surface. Preferably, all sections should be taken as nearly as possible at right angles to the surface, as this admits of obtaining a more exact relation of the epithelium to the underlying structures.

In conclusion, I would again point out that the final summing up of the nature of a new growth in the larynx must remain with the clinician.

FATTY STREAKS IN THE INTIMA OF ARTERIES.

By OSKAR KLOTZ and M. F. MANNING.

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FATTY STREAKS IN THE INTIMA OF ARTERIES.[1]

By Oskar Klotz and M. F. Manning.

From the Pathological Laboratories, University of Pittsburg.

With a view of determining the earliest stages of the arterio-sclerotic process our attention was attracted to those minute yellow streaks and dots which are so frequently observed in the arteries of young individuals. It is quite useless to argue the questions concerning the development of intimal scleroses if we study and discuss the late stages of the disease alone. We have ourselves fallen into this error, but, as has been recently pointed out, if we wish to gain a true insight into the complex question of arterio-sclerosis we must attempt to follow the lesion from its earliest beginning. This offers many difficulties, especially in the study of human material alone, while the relation of certain artificially induced arterial diseases in animals to those in man is not at all times evident.

Thus the problem reduces itself to one of the study of the many minute changes occurring in the walls of the arteries, in an attempt to find in one or more of them a succession of changes leading from the early and minute damage to the fully developed arterial lesion. It is well to point out that in studying such a lesion or lesions the successive stages are observed in the vessels from the different individuals, and possibly or even probably those individuals have not suffered the same disease or diseases of like severity as the preceding. The observer can therefore offer very little information from a single specimen of an artery as to the factors at work in the given lesions.

The type of disease which we have under discussion does not, at first sight, appear to have any bearing on Thoma's discussion of arterio-sclerosis. We are nevertheless drawn into direct contact with his work when, as we will show later, the outcome of some of these lesions with early fatty streaks is a condition which is indistinguishable from the later stages of true endarteritis. Thoma has recently reiterated his view concerning the arterio-sclerotic process. He still believes that the thickening of the intima by connective tissue is dependent upon the slowing of the blood current. Exactly in what

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manner the slowing of the blood stream acts upon the intima, and more particularly the connective tissue, he does not state. He suggests that the slow current may be associated with a poorer metabolism, that the stagnant metabolic products may irritate, or that the alteration of the current too may have a tugging action on the walls of the arteries. We must concede that these are all possible; but we must further indicate that each of these factors may be called into play without any previous alteration in the arterial wall, and particularly in the media. Thus it is obvious that the different postures of the body have an enormous effect in altering the hydrostatic conditions of the circulation. It is true, as Thoma indicates, that under certain conditions of the rate of flow of the blood when properly balanced with the peripheral resistance, the current of the blood is axial and the outer boundary of the stream is more or less at rest. It may be that with all the conditions given the plasmatic layer resting upon the inner circumference of the artery is immobile. That state, however, is changed immediately with the new conditions in which any one of the factors is altered. Thus the natural dilatation of the peripheral arteries in vasomotor inhibition will alter the relation of the lumen of an artery to the quantity of blood which is supplied to it. Muscular exercise constantly influences the relative size of the arteries, both by the direct excitation of the arteries and by muscular pressure on various vessels. Again, the alteration in the viscosity of the blood will tend to alter the rate of flow of the blood even when all the other factors determining the rate are kept constant. It is evident, then, that the circulation may readily undergo many changes in the rate of flow without any preceding structural alteration in the artery. True it is that the majority of these variations in the blood flow are transient; still, the recumbent position for recurrent periods of eight hours' sleep at a time must alter the hydrostatic conditions in the aorta very greatly. Moreover, the fallacy of these surmises, that local or more widespread slowing of the blood current, developing upon medial dilatation, is invariably the cause of connective-tissue development in the arteries, can be indicated by experiments and observations.

This study concerns itself only with processes in the intima of the arteries which are *degenerative* from the beginning. We wish to differentiate clearly such lesions from those which may begin as *productive* lesions on the surface, and which later develop into lesions having more or less degenerative characters about them. The beginning of each type can be clearly differentiated during the early stages of their development, while, later, much difficulty may be experienced in determining the nature of the earliest process.

The observations in this study were made on the arteries of a series of cases ranging in age from 1 to 73. The majority of the cases, however, were between the ages of 20 and 30. The vessels were obtained at autopsy, where they were carefully examined for macroscopic evidence of superficial fatty streaks. Histological examination was then also undertaken, the specimens being cut frozen or in paraffin. For our purposes the freezing method was mainly used, although for cell study the thinner paraffin sections were more satisfactory.

The vessels from various parts of the body were examined, but it was soon found that particular attention had to be concentrated upon the aorta and the vessels arising at the arch. In all instances the changes when present were found in these arteries, and of these the aorta showed the greatest frequency of the lesion. A few instances were observed in which fatty changes were alone present in the carotids, and these changes were noted, as Chiari has pointed out, at or near the bifurcation. This author has found lesions at the bifurcation of the common carotid in individuals under twenty-five years of age where no changes were to be noted in the aorta or other vessels.

It is unusual to have a wide distribution of this superficial fatty lesion in the peripheral arteries. Changes do occur in many arteries simultaneous with fatty streaks in the aorta and carotids, but these changes are not of the same character as the fatty lesions, although both may have the same etiological factor. Thus small pearly thickenings of the intima were observed in the peripheral arteries, particularly in the renal and mesenteric arteries, while only yellow streaks were found in the aorta. In some of the older individuals there were easily recognisable old processes in the outer coats of the arterial walls, while the more recent changes were seen on the inner surface of the intima. Nodular and pearly thickenings around the mouths of the intercostal arteries were often observed in older persons, while in the same vessel the fatty streaks were arranged longitudinally in the thinner portions of the artery. Old calcareous deposits were present in a few cases, but never close to the more recent fatty streaks.

There are definite age periods when fat in superficial streaks is most commonly found in the intima. Between the ages of 20 and 30 the condition is very frequent; it is unusual before the age of 10 or after the age of 50. The frequency of this condition, therefore, does not increase with advancing age, as, apparently, does nodular arterio-sclerosis. We have observed the lesion four times before the age of 10 (6, 8 (twice), and 9 years respectively); each of these was found in an autopsy on a scarlet fever patient.

Naturally the most interesting cases for study are young individuals. In them the various causative factors are more readily approached, particularly when the individual has been robust until the final illness. It might not be safe to suggest that the final illness was the agent leading to the changes found in the arteries at death, but when we find with such regularity that typhoid fever is accompanied by fatty streaks in the aorta and vessels of the neck we cannot but feel that the infection had something to do with the lesion.

Ages.	Number of Cases Examined.	Frequency of Fatty Streaks.
1–10	16	4 cases
11–20	12	8 ,,
21–30	15	12 ,,
31–40	22	7 ,,
41–50	15	4 ,,
51–73	10	1 ,,

In our experience these superficial fatty lesions were found most frequently in cases which had died of typhoid fever. In this disease it could be looked for with fair certainty in all individuals under 30 years of age. Frequently the condition was very marked, and it was only very infrequently that a considerable yellow streaking of the descending thoracic aorta was not found. In our records on typhoid fever in which the lesion was looked for at autopsy we have noted its absence in two cases only. This covers a series of thirty-five cases of typhoid fever. At one time it was thought that the intensity of these fatty streaks suggested the diagnosis of typhoid fever or a closely related infection. This, however, does not hold true in all cases. The lesion in typhoid is most frequently seen in the descending aorta and occasionally in the mesenteric artery. These lesions varying in intensity are also to be observed in pneumonia, in acute osteomyelitis, puerperal endometritis, scarlet fever, pernicious anæmia, and severe cachexias. We have found, however, that the frequency and intensity of the condition in these last two diseases is much less than for infections, particularly severe septicæmias.

On the other hand, in cases of accidental sudden death, two of typhoid fever and one of toxæmia of pregnancy all before the age of 20, and three of scarlet fever before the age of 10, there was no evidence of fatty change of the intima.

In general, the appearance of the condition is fairly uniform. The lesion consists of narrow yellow lines running longitudinally and lying close beneath the endothelium. When closely examined these fine streaks or lines are slightly raised above the inner surface of the vessel. At times the lines seem to be made up of multiple small points or dots which have, in part, coalesced. Besides these yellow streaks, many fine pale lines and dots are found scattered between them. The position of the lesion is fairly constant. They are almost always found along the posterior wall of the aorta, lying between the pairs of intercostal arteries or close to their outer borders. The anterior and outer walls of the aorta are usually free from change. There are instances in which the process extends beyond the posterior wall and becomes quite diffuse. Nevertheless, the most intense lesions are to be looked for along the posterior border of the aorta.

A similar type of lesion is also seen at the base of the aorta just above the aortic ring. Here the yellow dots do not take any definite arrangement, but seem to lie more transversely to the vessel than in the descending thoracic aorta. Similar dots and streaks with a partial longitudinal arrangement are found in the large vessels arising from the aorta, and occasionally they are seen in many of the branches of the vessels of the abdomen.

All these lesions, when seen during the acute stage of the disease which apparently gives rise to them, are found to be immediately beneath the endothelial lining. In some instances the small elevations can be incised with a knife and some fatty material expressed from them. On the other hand, when the lesion is seen toward the end of the causative disease they appear to have a thicker layer of cells covering them, and at times there is a fairly smooth and glistening membrane forming a pearly nodule. Still other lesions are observed in which the yellow streaks are only slightly raised above the surface, and where the degenerative process appears to lie at some little distance below the surface lining.

In a microscopical examination of the vessels showing the superficial fatty streaks of the intima we have found that the process may begin in one of two places. In some instances, changes with the early deposit of fat are seen in the subendothelial layer of connective tissue alone. In other instances this layer may show little or no change, but the fatty change may be confined to the musculo-elastic layer, or what is more common the degenerative changes are found in both layers of the intima. We have noted that in either case an œdematous appearance develops early in the intima in both its superficial and deeper portions. The connective-tissue cells stand widely apart, and there is an indefinite granular material lying in the interstitium of the cells. The connective-tissue cells no longer occupy any particular relation to each other or to the direction of the lumen. In some instances the œdema of the strip of the subendothelial connective tissue makes the layer appear less cellular. On the other hand, it was particularly noted that in a later stage, when fat was being deposited in the tissue, the number of cells to the part increased considerably. The nuclei of these cells were usually oval and stained quite intensely. The cells developed fibrils which stained like those of connective tissue. Beside this were found a few widely scattered lymphocytes in and about the area of degeneration.

The fat earliest deposited in the subendothelial layer lies within the cells. Cells having the same character as the mature connective-tissue cells of this layer are seen to have an accumulation of fatty material, often extending in a wedge-shaped mass at one or both ends of the nucleus, and for some distance from the nucleus. This fat first appears as fine discrete granules, and in cells containing a greater quantity of this material the fat is aggregated into larger masses or globules.

We have not been able to demonstrate that in this process of cell proliferation of the intima any of the fat-containing cells have been derived from the endothelial layer. We have observed repeatedly that the lining endothelium which so commonly is shed after death has produced a narrow layer of loosely attached cells upon the surface. However, there was no evidence that these proliferated cells entered into the formation of the thickened and fatty layer of the subendothelium.

In the later stages of fat accumulation within the subendothelial cells it is noted that these cells retain their shape and the nucleus remains in the centre until the cell substance is widely distended, almost to bursting, with the accumulation of fat. Cells of various shapes are seen—oval, spherical or spindle shaped. These same spindle cells when cut transversely appear fairly circular. In the still later stages the cells with their nuclei disappear and leave the fat in the interstitial spaces. Specimens are not infrequently seen in which a few circular or spindle-shaped spaces are filled with a fatty material. This fat then lies between the tissue fibres and cells, and naturally in this condition it is difficult to state its exact origin. However, as the process of gradual accumulation of lipoid substances can be observed, and as the degeneration of the cell may also be followed, it seems fair to assume that the free fat comes from cell disintegration.

During this period, in which the subendothelial cells show the accumulation of fat, the elastic fibres in the hyperplastic zone show the faint yellow tinge of a fatty change. At first the colour change appears to be diffusely spread through the fibre without the appearance of granules. Later, fine granules appear when it is difficult to determine whether these are within or only on the surface of the elastic fibres.

The changes in the musculo-elastic layer are of quite similar order to those in more superficial portions of the intima where changes, as above described, are being brought about. In the former tissue there is evidence that the interstitial spaces become wider and are filled with a homogeneous or finely granular débris. The cells in the musculo-elastic layer appear more prominent, so that this band of muscle fibres is more readily recognised than under normal conditions of the vessel. Whether an actual increase in the number of muscle cells takes place is hard to say, but it is apparent that the longitudinal muscle fibres are much more prominent and occupy a wider zone. The degenerative changes, which are recognised by the fat stains, occur in the muscle cells by the accumulation of fat granules in a greater or less quantity. The fine elastic fibres which are present between the muscle cells and the muscle bundles are also found to be attracting a fatty substance to them. These fibres eventually appear quite granular with the yellow lipoid bodies. Where the degeneration is advanced the muscle fibres become less numerous, and masses of fat granules are found to lie in the positions which the muscle cells formerly occupied. In no instance have we observed evidence of inflammatory cellular infiltration in the musculo-elastic layer during these processes.

The affected area of the superficial intima occasionally showed a slight reaction of proliferation with scattered lymphocytes. An acute inflammatory reaction was not observed either in or about the tissues showing the fatty change. On the other hand, the vasa vasorum of the adventitia and of the outer zone of the media were repeatedly observed to have a cellular infiltration about them. Lymphocytes and plasma cells were most abundantly present, with stray polymorpho-nuclear leucocytes. In these situations, however, there was no evidence of the accumulation of fat in the tissues. The media and adventitia showed no other evidence of change which could be associated with the condition arising in the intima. In fact, in young individuals no alteration of any other tissues was observed, while in adults, and in particular those beyond middle age, varying lesions were observed, common for this period of life, in one or other of the arterial coats. In no instance was a former lesion found to influence the character of the recently acquired fatty streaks.

One feature, however, of sclerosed arteries was evident, that the vessels with former intimal sclerosis, either nodular or diffuse, rarely showed fatty streaks even when the patient had suffered from a disease which in the young adult would have been followed by these lesions. It would appear that where the subendothelial layer had been thickened with the production of connective tissues it no longer reacted to irritants as formerly. Degenerative changes do, of course, develop in the thickened fibrosed intima, but these occur in the progressive process of intimal sclerosis.

The fat, as we have observed, is at first deposited within the living cells and in the elastic fibres. Later, free fat is found between the tissue cells and lying as fine droplets upon the different fibres. In some of these deposits anisotropic globules, like myelin, were seen. The fat and fat-like substances could be dissolved from the tissues by alcohol and ether, while no lipoid substances insoluble in these solvents were observed. All of the fat stained after the manner of neutral fats.

From our observations it appears quite definite that fat may be deposited in streaks either in the subendothelial layer or in the deeper musculo-elastic layer. Or again, both layers may be affected at the same time and the lesions coalesce, so that a condition of "fatty degeneration" extends from the endothelial layer to the innermost lamella of the media. What process governs the laying down of fat in this or that layer of tissue, or why certain areas in the arteries are the sites of predilection, has not been determined. The main interest that attaches itself to the study is the relation of the fatty streaks of the aorta to the more severe and extensive atheromatous processes.

We have repeatedly observed that as fat accumulated in the subendothelial or musculo-elastic layer, the superficial portion of the intima became thicker and formed a small nodule of flat and parallel cells over it. This was particularly evident in those cases where the process had developed to the degree in which the fat-laden cells were destroyed and liberated their contents into the interstitial spaces. The degree of proliferation varied greatly, but the same compact mass of an almost hyaline-looking tissue was always produced. We were not able to determine whether these new cells were of endothelial origin or were derived from the layer of subendothelial connective tissue immediately beneath this.

As we study these lesions in succession we come upon some in which we can no longer distinguish the sequence of events. The subendothelial thickening forms a definite nodule of long and narrow spindle cells with much hyaline material between them, in which delicate elastic fibrils are found. Below this proliferative nodule is an isolated or diffuse fatty degeneration of the musculo-elastic layer or of the hyperplastic layer. This process, even in the presence of fatty streaks of the intima, makes it difficult to make a positive statement as to whether or no the degenerative condition has been primary. We believe that some, at least, of these lesions have their origin in a primary degeneration of the deeper portions of the intima, with a secondary proliferative reaction close to the endothelial lining.

Our findings are in accord with those of Jores (1903 [4]), Askanazy (1907 [1]), Benda (1909 [2]), and others.

These observers believed that the superficial fatty streaks of the intima were closely associated with advanced arterio-sclerosis. Jores was the first to show that the small white or yellow streaks of thickening found in young individuals were the beginning of arterio-sclerosis of the aorta. He found much of the fatty change in the musculo-elastic layer, where the elastic fibres in particular were altered in the degenerative process. The thickening of the layer on the surface was a condition arising secondarily to the deeper degeneration. Askanazy, while he admitted that the fatty streaks might progress to definite atheromatous processes, believed that many of them disappeared without advancing into the more serious lesion. On the other hand, Thorhorst (1904 [7]) and Hallenberger did not consider the fatty streaks of the intima as important factors in the production of arterio-sclerosis.

They point out that minute thickenings may be observed in the intima without fatty change.

Thorel (1910[8]) points out that the small fatty areas produce a change in the character of the inner layer of the artery which alters its elasticity and which must be recognised as a definite manifestation of a progressive tissue degeneration. In recognition of this early and progressive change, which combined with it some characters of sclerosis, Marchand (1904[5]) applied the name of athero-sclerosis.

The frequency of these fatty lesions in the vessels of young individuals with acute diseases, and their absence, microscopically, after a year or two, demands some explanation, if we consider they have any association with true arterio-sclerosis later in life. There can be no doubt but that many of these superficial lesions disappear almost entirely and leave the artery in an elastic condition equal to normal. We do believe, however, that although the débris and fat of the degenerative process may in some areas be fully absorbed, the proliferated cells of the subendothelial layer are permanent, and although they do not form isolated nodules assist in producing a more or less diffuse thickening of the intima. On the other hand, the more severe lesions, which have caused the destruction of cells in the musculo-elastic layer and also in the hyperplastic layer of the intima, have a more extensive reaction in the subendothelial layer in producing localised nodular thickenings which are permanent and indistinguishable from endarteritis nodosa. In them, however, the products of degeneration are not readily absorbed, so that these early thickenings of "endarteritis" always have fat and débris in their deepest portion. Such areas have all the characters of chronic endarteritis with early atheroma, and there is no reason to believe that the process cannot go on to atheromatous ulceration.

It is evident, from our finding, that it would be most difficult to determine the process of development of an atheromatous area after it was fully established. From our observations and those of others it is seen that an atheromatous process may be a degenerative lesion from the very beginning, with more or less proliferative reaction above it. On the other hand, Jores and others have determined that the primary intimal hyperplasia may be followed by fatty and other degenerations. We are not familiar with any definite points by which a well-developed atheromatous process may be recognised as coming from one or other process.

In general, the situation of the fatty streaks about the intercostal vessels is the same as the nodular endarteritis. Each is commonly found distributed on the posterior surface of the descending aorta. The thickening of the actual mouths of the intercostal vessels is a process which not infrequently has the condition of fatty streaks of the intima as a forerunner. In such cases the nodular endarteritis is a secondary result of an irritative process.

It is evident from these observations that there is a direct relation between acute infective diseases and progressive lesions in the intima of the larger arteries. These lesions, though apparently of little account at the beginning, may become autochthonous and develop into definite nodular endarteritis with atheroma. Thus even when the initial factors leading to the fatty streaks are removed a vicious process is established which may lead to a nodular arterio-sclerosis or atheromatous ulceration.

We have found no evidence that before the development of the fatty streaks of the aorta a degenerative or other condition in the media is associated with the growth of connective tissue in the intima; but there is every indication that the production of tissue in the intima is the result of a direct irritation of that tissue by the presence of infection or toxins or of the stimulation by the products of a primary degeneration in that layer.

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STUDIES IN ARTERIOSCLEROSIS.

Much has appeared in the literature in recent years upon the etiology and process of development of arteriosclerosis. Many observations have been made upon the human subject also in experimental animals, of points co-relating certain factors with the production of diseases in the arterial tree. In some instances these factors have been carefully studied by competent observers and in many instances the results have been verified by others.

The gathering of facts concerning arteriosclerosis is quite simple-the interpretation of these involves much difficulty. In carrying out any experiment or in offering reasons for a given result, we are constantly reminded of the manifold factors which enter a given experiment or which are naturally present. Often our experiment on animals only

induces altered conditions which indirectly bring about the result we are seeking. That the greatest care must be exercised in drawing inferences from animal experimentation is well illustrated in studies upon arteriosclerosis.

Recently Levin and Larkin' have published the results of their experiments on dogs, in which by producing an arterio-venous anastomosis between the external jugular vein and the external carotoid artery, they arrive at the sweeping conclusion that "arteriosclerosis can not be artificially induced in a previously healthy blood-vessel by a change in the blood pressure alone." To this type of conclusion we must take exception.

Levin and Larkin, experimenting on ten dogs, joined the external cartoid artery to the external jugular vein. In two of these dogs thrombosis occurred close to the line of suture in the vessels. All but two of the remaining eight received injections of adrenalin

at varying periods. These eight dogs, which form the positive results and from which the above statement respecting arteriosclerosis was made, were allowed to live 102, 58, 72, 15, 124 and 58 and 44 days, respectively.

No one who has studied diverse pathological lesions, will deny that the distribution of various lesions in organs is not uniform in the animal world. Man is particularly subject to lesions of the circulatory system - a condition not so frequent in lower animals. Rabbits and horses occasionally suffer from arterial lesions more often seen in the older animals and in certain breeds. Dogs and cats rarely develop lesions in the arteries, even under most trying circumstances.

This varying susceptibility still awaits an explanation, but in the face of our ignorance in the matter, we must assume the greatest care in drawing broad conclusions or in proposing far reaching principles. Negative at varying periods. These eight dogs, which form the positive results and from which the above statement respecting arteriosclerosis was made, were allowed to live 108, 32, 76, 15, 152 and 52 and 41 days, respectively.

No one who has studied diverse pathological lesions, will deny that the distribution of various lesions in organs is not uniform in the animal world. Man is particularly subject to lesions of the circulatory system - a condition not so frequent in lower animals. Rabbits and horses occasionally suffer from arterial lesions more often seen in the older animals and in certain breeds. Dogs and cats rarely develop lesions in the arteries, even under most trying circumstances.

This varying susceptibility still admits an explanation, but in the face of our ignorance in the matter, we must assume the greatest care in drawing broad conclusions or in proposing far reaching principles. Experi experimental results for the dog have no positive bearing upon experimental facts observed in other animals.

Much criticism is offered against the use of the rabbit for experiments upon the circulatory system. The comment has been that spontaneous arterial disease occurs in this animal. And yet none of the critics offer any suggestion for the cause of this spontaneous lesion! Properly selected animals and controlled experiments can reduce the error of "spontaneous" disease to almost a vanishing point. The very feature, in the rabbit, of readily reacting in its arterial tree to different noxae, determines its usefulness for studying the diseases of the circulation.

In the experiments of the above-cited authors, the observations were made upon the venous segments of the anastomosis. Here although in only some of the animals the vein was noted to be dilated, it is concluded that

an increased blood pressure existed in all. It is not at all clear to what extent the blood pressure was increased when the external carotid and external jugular were united. With the free abastomosis which exists (varying much in individual animals), between the venous channels of the neck, it is possible that an increase of pressure exists for only a short period after the successful anastomosis.

It is further to be pointed out that various observers have recorded that periodic and intermittently increased blood pressure have quite a different effect upon the blood vessels than a constant and continous one. The periodically increased pressure is found commonly in man, and if we may draw any conclusion from the finding of occupation sclerosis (right radial sclerosis in the blacksmith, femoral sclerosis in the policeman), it is that the periodic increase of pressure lends

to degenerations and sclerosis in the arteries.

Finally, but of primary importance, the results of observations on veins can not be utilized in drawing conclusions about arteries, as has been done by Levin and Larkin.

Oskar Klotz.

University of Pittsburgh,
February, 1911.

Journ. Exper. Med. 1911, X111, P. 24.

See Carrell and Guthrie, "Surg. Gyne. & Obstet." 1906, Vol. 11; and Watts, Bull. Johns Hopkins Hosp. 1907. Vol. XV111.

ARTERIO-SCLEROSIS AND ITS RELATION TO CHANGES IN THE MEDIA OF ARTERIES.

The group of diseases of the arterial walls comprised under the general term of atheroma and arterio-sclerosis is still somewhat ill-defined, in spite of the large amount of pathological and experimental work which has been devoted to its study. An interesting review of this subject, based upon personal observations as well as upon a study of the literature, is given in a monograph by Dr. Oskar Klotz,[1] of which we have received a copy. He commences by stating that it is now generally recognized that this disease, instead of being generalized, may be localized to the arteries of one particular organ, that it may involve one particular type of artery only, and that it may be limited to one or other zone of the arterial coat.

He maintains that the recent study of Jores and others have established a satisfactory basis for classification of the intimal changes, but that the lesions of the media are more obscure, so that there is still much confusion both as to their nature and mode of development and as to their relationship to the intimal changes. In opposition to the views of Jores, who maintains that arterio-sclerosis is essentially an intimal disease, Dr. Klotz includes under this term any change in any of the three coats of the artery which leads to a thickening or hardening of the vessel wall. These changes he classifies into productive and degenerative, and further subdivides according to the nature of the resulting lesions in the vessels. He admits that, employed in this manner, the term arterio-sclerosis becomes generic and not specific, and requires a qualifying adjective to distinguish the individual or special forms.

The term atheroma has been variously used by different authors; for Dr. Klotz it is a degenerative change followed by calcification beginning it, and usually confined to, the intima. It may advance into the media, but seldom, if ever, originates primarily in this coat. He gives an interesting review of the histology of arteries and of the functions of the media, and emphasises the facts that this coat is the mainstay of an artery, and that upon its integrity depends the resisting power against intra-vascular pressure. Dr. Klotz differentiates medial arterio-sclerotic processes from other conditions leading to thickening of the arteries, and he divides them tentatively into productive and degenerative varieties. Certain forms he regards as meriting special recognition, one being syphilitic mesaortitis, which can be recognized both by its macroscopical and histolical characteristics; a second being

Moenckeberg's arterio-sclerosis, which is a degenerative condition of the media of the peripheral arteries following upon intermittent arterial overstrain. The principal factors causing disease of the media are infections, poisons, work, and old age. The effect of any of these depends upon the histological structure of the artery affected and upon its function. The same agent may give rise to several kinds of arterio-sclerotic processes, but it must be remembered that the presence of disease in one system of vessels must not be taken as indicating disease in another arterial system, and that medial sclerosis is often present without intimal sclerosis in the same vessel. Dr. Klotz shows that aneurysms are directly dependent upon the diseases of the media of arteries, and that the nature of the aneurysm is determined by the character of the medial disease- e. g., syphilis is the most important factor in the production of chronic

mesarteritis and aneurysm of the aorta, while medial weakening from causes other than syphilis are more frequently associated with aneurysms of the peripheral arteries. Dr. Klotz's works upon the genesis of arterial disease is well known, and we welcome this review of the subject of diseases of the middle coat as a notable contribution to the scientific study of medicine.

I. Arterio-sclerosis, Diseases of the Media and their relation fo Aneurysm. By Oskar Klotz, M.B. Tor., M.D. C.M. McGill. Publications from the University of Pittsburgh Medical School, 1911.

The Lancet- 1911- June 7th, - p. 1655.

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